FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

# VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

April 6, 2011

Hilton Hotel Washington DC North/Gaithersburg
620 Perry Parkway, Gaithersburg, MD



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P R O C E E D I N G (9:00 a.m.)

**Agenda Item: Open Session**

DR. FERRIERI: Good morning. I am Patricia Ferrieri. I am from the University of Minnesota Medical School. I would like to welcome everyone to this meeting. If we could take our seats so we can proceed? At this point, I would like to ask Don Jehn to make some announcements before we proceed.

MR. JEHN: Good morning, everybody. I am Don Jehn, the designated Federal Official for today's meeting of the Vaccines and Related Biological Products Advisory Committee.

I would like to welcome you all to this 126th meeting of the Advisory Committee. Dr. Ferrieri is our acting Chair for the meeting and we welcome her. Today's session is open to the public, except between approximately 10:50 AM until 11:30, during which we will have a closed session. Tomorrow's session will be completely open to the public.

These sessions are described in the Federal Register Notice of March 14, 2011. I would like to request that everyone please check your cell phones and pagers and make sure they set off or in a silent mode. Now, I would like to read into public record the Conflict of Interest Statement for today's meeting.

**Agenda Item: Conflict of Interest Statement**

MR. JEHN: The Food and Drug Administration (FDA) is convening the April 6-7, 2011 meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the industry representative, all participants of the Committee are special government employees (SGEs) or regular Federal employees from other agencies and are subject to the Federal conflict of interest laws and regulations.

The following information on the status of this Advisory Committee's compliance with Federal ethics and conflict of interest laws, including, but not limited to 18 US Code 208 and 712 of the Federal Food, Drug and Cosmetic Act, are being provided to participants at this meeting and to the public. FDA has determined that all members of this Advisory Committee are in compliance with the Federal Ethics and Conflicts of Interest Laws.

Under 18 US Code 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees, who have financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Under 712 of Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the Committee of their essential expertise.

Related to the discussion of this meeting, members and consultants of this Committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for the purposes of 18 US Code 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, CRADAs, teaching/speaking/writing, patents and royalties, and also primary employment.

For topic one in the open session, the Committee will hear an overview of the research programs in the Laboratory of Bacterial Polysaccharides, Division of Bacterial, Parasitic, and Allergenic Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, FDA. This overview is a non-particular matter and presents no actual or appearance of conflict of interest.

For topic two in open session, the Committee will discuss and make recommendations on the use of immunological markers for demonstration of effectiveness of meningococcal serogroups A, C, Y, and W-135 conjugate vaccines administered to children less than two years of age. This is a particular matter involving specific parties.

For topic three in open session, the Committee will discuss and make recommendations on approaches to licensure of meningococcal serogroup B vaccines. This is a particular matter involving specific parties.

Based on the agenda and all financial interests reported by members and consultants, no waivers were issued under 18 US Code 208 B3 and 712 of the Food, Drug, and Cosmetic Act. Dr. Margaret Rennels is serving as the industry representative, acting on the behalf of all related industry. She is employed by GlaxoSmithKline in Washington D.C. Industry representatives are not special government employees and do not vote.

In addition, there may be regulated industry and other outside organization speakers making presentations. These speakers may have financial interest associated with their employer and with other regulated firms. The FDA asks in the interest of fairness that they address any current or previous financial involvement with any firm, whose product they may wish to comment upon. These individuals are not screened by the FDA for conflicts of interest.

This Conflict of Interest Statement will be available for review at the registration table. We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationship that you may have with any affected firms, their products, and, if known, their direct competitors. Thank you.

DR. FERRIERI: Thank you, Don. As I mentioned, I am Pat Ferrieri from the University of Minnesota. It is a great please, always, to be here with FDA. I would like to begin by having introductions of everyone around the table. I will start with Dr. Gellin, please.

DR. GELLIN: Thanks, Pat. Bruce Gellin,

Director of the National Vaccine Program Office at HHS.

DR. CHEUNG: Ambrose Cheung, Microbiology, Dartmouth Medical School.

DR. GILBERT: Peter Gilbert, Vaccine and Infectious Disease

DR. APICELLA: Mike Apicella, Department of Microbiology, University of Iowa.

DR. RENNELS: Margaret Rennels, industry representative.

DR. MCINNES: Pamela McInnes, National Institutes of Health.

DR. SCHOOLNIK: Gary Schoolnik, Stanford University.

DR. TACKET: Carol Tacket, University of Maryland.

DR. DURBIN: Anna Durbin, Center for Immunization Research, Johns Hopkins University.

DR. GRAY: Greg Gray, University of Florida.

DR. DEBOLD: Vicky Debold, National Vaccine Information Center, consumer representative.

MR. JEHN: I would just like to make a note that Dr. Romero and Dr. DeStefano, committee members, are not attending this meeting. Also Dr. Wharton is not here, also, for this meeting.

DR. FERRIERI: Thank you, Don. I think we will proceed then with the discussion of the site visit and the presentation from the Laboratory of Bacterial Polysaccharides. This is under Topic 1. Our first speaker will be Dr. Carolyn Wilson on an overview of the research/site visit process from CBER.

**Agenda Item: Topic 1: Presentation of Laboratory of Bacterial Polysaccharides, Division of Bacterial Parasitic, & Allergenic Products, Office of Vaccines Research and Review, center for Biologics and Research**

**Agenda Item: Overview of Research/Site Visit Process, Center for Biologics Evaluation and Research (CBER)**

DR. WILSON: Welcome to the Committee members. Now can you hear me? I wanted to just give a brief overview, a little bit about our center, what we regulate, and the process that we use to manage our research resources and how the site visit process fits into that.

Our mission is to ensure the safety, purity, potency, and effectiveness of biological products, including vaccines, which, of course, is the topic of your Committee, blood and blood products, and cells, tissues, and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions, or injury.

Our vision is to protect and improve public and individual health in the US and, where feasible, globally. To do this, we facilitate development, approval, and access to safe and effective products and promising new technologies and strengthening our Center as a preeminent regulatory organization for biologics.

Importantly, we try to apply innovative technology to advance the public health. I think that is where our research programs play a critical role in making sure we are looking at being ready for evaluating innovative technology and also applying it where it makes sense.

We regulate a number of very complex products. Of course, you are very familiar with vaccines and the complexities associated with those. We also regulate all of the blood supply, blood components, and derivatives, allergenic products, which I know you are also familiar with, cell and gene therapies, xenotransplantation products, and human tissues, as well as a variety of related devices.

The role of research plays a very important role for us to be able to fulfill our regulatory mission. This graphic helps to just kind of give you an example of how it is applied. Of course, everything sort of starts and ends with the public health issues. There is a public health problem that needs to be addressed through development of a new medical product. That new product or perhaps an existing product that is being modified or being applied new technology may sometimes result in novel regulatory challenges.

Those challenges represent things that are missing. Things like lack of appropriate animal models, inappropriate assays to assess potency, lack of standards or reference materials to be able to assess product safety or efficacy. That is where our research program can play an important role, through both the process of discovery and development of new tools, methods, new reference materials and standards.

Once we have that better information and that data, that provides us an ability to make science-based regulatory policies and decision making. By having better guidance to sponsors, that then allows us to get improved data coming into submissions and allows us to have a better informed benefit/risk decision making.

At the end of the day, what we hope is a licensed product that is both safe and effective that will have a positive impact on the initial public health problem.

Our organization is organized with seven offices. The Office of the Director is where Deputy and Associates reside. The Petri dishes are sort of cross-cutting offices that support the entire organization: Management, Communication, Outreach and Development, Compliance and Biologics Quality. Then the epindorph tubes, those represent our research divisions. Our divisions where research goes on are Biostatistics and Epidemiology, Cellular, Tissue, and Gene Therapies, and obviously Vaccines Research and Review, Blood Research and Review.

Our facilities provide a number of support opportunities for our scientists. We have a biotechnology core facility, which, as you can see, provides a number of different techniques and methods that are provided to our investigators on a fee for service basis. We have some limited core support for some other technologies like flow cytometry and confocal microscopy. State of the art vivarium with procedure rooms that supports work with rodents, as well as non-human primates. BSL-2 capacity for infectious agents.

We also have BSL-3 and animal BSL-3 laboratory capacity.

Our scientific expertise across the Center really comprises a very diverse set of scientific disciplines. We have experts -- you will hear about some of this today -- in novel technologies, such as NMR, mass spectrometry, flow cytometry, high throughput sequencing. We have, as you would expect, a very deep expertise in microbiology, parasitology, bacteriology, and virology. We also have very intense immunology expertise, biochemistry and molecular biology and cell and developmental biology. Having so many different disciplines represented provides a very rich environment for cross-disciplinary interactions and collaborations.

The other thing, which you may not be aware of, is our researchers are what are called researcher-regulators. What this means is that our research staff also do all of the same review activities that full-time regulators do. That means that they are reviewing submissions to the agency, going on inspections, writing guidance documents.

As you will see later in the next two days, they participate in advisory committees, presenting regulatory topics to the Committee, organizing workshops, and so on. Because these same people are involved in regulatory activities and doing research, this ensures that we are really using our expertise in the most relevant and purposeful way.

Our research management involves a series of really iterative processes. You can start really anywhere on this diagram. I will start with identification of regulatory and public health needs, which obviously should drive our Center and Officer priorities. Based on priorities then, the investigators align their programs to meet our identified research priorities, which should be addressing those regulatory and public health needs.

A critical component of all of this is this opportunity to obtain external review and input. That is where the site visit provides us an additional eye on whether or not we are really using our research resources in an optimal manner.

We develop research priorities. I am not going to read through these for you for the sake of time, but they are in your handout. These first three are really relevant to our laboratory-based program. The second three are more relevant to our biostatistics and epidemiology group.

As I mentioned, we have cyclic review every four years. This consists of both an internal process, as well as the external process that is through the site visit. In addition, we also have an annual review where each year that we have through a database, each PI provides an update of their work, a progress report, future plans, their budget requests, up-to-date publications, presentations, other relevant output, such as guidance documents. Advisory committee workshops that may be relevant to their program are also collected.

That information is reviewed by the Lab Chief, Division Director, Associate Director for Research within the Office, and the Officer Director. They are looking specifically at the relevance of that research program to the state priorities, the productivity of the program, and the quality. Then the funding is allocated in accordance with those findings.

So the site visit report, the process that we are doing today is the site visit has come to the Center and spent a full day reviewing our program, in this case the Laboratory of Bacterial Polysaccharides. They have generated a draft report. That site visit committee is a subcommittee to this advisory committee. What we are asking for you today is to review that draft report, provide your input, and vote on whether or not you would approve it or if modifications need to be made.

The report is very important for us, again, as a research management tool, as well as for the investigators, themselves. It is used by our Internal Peer Review Committee for promotions and conversions and the four year cyclic review. The PIs obviously take the input very seriously for improving their own program. Then management also looks very careful at the recommendations to make decisions about resource allocations.

Finally, I just want to thank the members of the site visit who came, as well as to you, today, for your additional input and evaluation. Again, this external review is really an important process for us to be able to make sure our research programs are on target, are of high quality, being productive, and fulfilling our regulatory mission.

Thank you for your attention. I would be happy to answer any questions.

DR. FERRIERI: Thank you Dr. Wilson. Are there any brief questions for Dr. Wilson from the table? Thank you very much.

We will move on then to our second speaker, Dr. Konstantin Chumakov, who will talk about an overview of the Office of Vaccines Research and Review.

**Agenda Item: Overview of Office of Vaccines Research and Review (OVRR), CBER**

DR. CHUMAKOV: Good morning. I will give a brief overview of the Office of Vaccines and our research programs. First slide, please.

The Office includes three divisions: Division of Bacterial, Parasitic, and Allergenic Products, Division of Viral Products, and the Division of Vaccines and Related Products Applications. The latter division is where the full-time reviewers are located. This division is responsible for review in response to applications that are filed by industry.

The two other divisions -- Bacterial Vaccines and Viral Products -- they are the home of our research-reviewers that Dr. Wilson mentioned. These divisions, besides doing their regulatory work, they are also involved in bench science. These two divisions, they have a total of 35 individual research programs that are led by senior investigators.

For administrative and management purposes, they are organized into labs. Here is the structure of the Division of Bacterial, Parasitic, and Allergenic Products. That has the Lab of Bacterial Polysaccharides that is the subject of today’s site visit review, as well as other labs -- Respiratory and Special Pathogens, Mycobacterial Diseases and Cellular Immunology, Enteric and Sexually Transmitted Diseases, and the Laboratory of Immunobiochemistry. As you see, these divisions cover the entire spectrum of products that are regulated by the Office, in terms of bacterial, parasitic, and allergenic products.

The mission of the office is to protect and enhance public health by assuring the availability of safe and effective vaccines, allergenic extracts, and other related products. Other related products also include probiotic -- live biotherapeutic products.

We accomplish this mission by review and evaluation, and taking appropriate actions for regulatory submissions filed by the industry, such as INDs, BLAs, amendments, supplements -- participate in inspections of manufacturing facilities and so on. The second arm is development of policies and procedures governing the review and development of new products. Last, but not least, is we conduct research that is related to the products that we regulate.

So why do we do research? What is the role of FDA research? First, the full FDA occupies a unique niche in the product development pipeline at the very end. We are the last safeguard on the way of biotechnology products before they reach the marketplace.

Also, FDA scientists are uniquely positioned to address some critical issues because we are familiar, both with scientific aspects, but also with the industry, having firsthand involvement in the regulatory process. Our scientists really are familiar with some things that perhaps are not as obvious to those researchers, who are in academia.

Finally, the important part of the reason for why FDA needs to conduct research is that the results remain in public domain. A lot of the issues that we address could be also addressed by the scientists in industry, but in this case that would be proprietary and not always benefiting their product line. I think it is very important for researchers in the public sector to be able to conduct this research that has an immediate relevance to safety and efficacy of vaccines.

The purpose -- what we expect from our research programs is that we address some issues that have immediate relevance to our regulatory actions. We often meet some challenges in regulatory activity that are best addressed by our scientists doing it in the labs, rather than requesting from the industry, again for the same reason that the results that will be obtained will be applicable to a broad range of products, not just one specific product.

We also develop new methods and we validate new methods for evaluation of safety and efficacy of vaccines. We develop standards and reference reagents, which is also very important for expeditious licensure of new products.

We also look at this program as a way to recruit and maintain a highly qualified cadre of scientists. To perform quality review, we also need people who really are on the top, on the cutting edge of new development in biotechnology. Allowing our researchers to practice their trade allows us to attract talented scientists and give them the opportunity to develop professionally.

Also, I think it is important that having highly qualified and respected scientists on FDA staff gives us additional clout with industry. It commands or it gives high respect to the Agency when the reviewers are really first class, world-recognized scientists.

It is a very difficult task to reconcile the investigator-initiated model of research that we strongly believe in and the very specific needs of the Agency. In order to make these two competing demands meet, we use a research management process that actually is shown on this slide. It is quite a busy slide, but essentially it is pretty straight forward.

Principal investigators are at the center of our research programs. They are researcher-reviewers so they are exposed to needs of regulatory process. They take advice and recommendations from site visits, advisory committees that participate in scientific conferences. They interact with their peers. They are very familiar with the issues.

They formulate their research problems on an annual basis, create their research proposals, which is discussed with lab chiefs, supervisors of principal investigators, then the portfolio of projects from each lab is then discussed with the Division Directors.

Finally, it reaches the Research Management Committee. This committee, actually, is composed from representatives from all divisions of the Office. Its purpose is first to formulate research priorities and also to review the balance of the research program to make sure that we cover most important things and there is no significant and unnecessary duplication.

So this Research Management Committee reviews the entire portfolio and then recommends either modifications or approval. Depending on the availability of funds and resources, this budget is approved.

The priorities of our research programs are based on three pillars. First, we address issues related to safety, efficacy, and availability of vaccine products. I will give you just a few examples of type of research that the Office conducts.

In the area of safety, we work on evaluation of purity of components in vaccines, including adventitious agents and cell substrate issues. We study utility of novel scientific technologies, such as genomics, proteomics, for evaluation of consistency of vaccine products. We create methods and models to study potential toxic effects of vaccines and their components.

We also study biomarkers of pathogenicity, which is related to the specific safety issues that lab vaccines have. Also, we study mechanisms of adverse reactions and ways to mitigate them and minimize the potential harmful effects of vaccines.

In the area of efficacy, we study pathogenesis to identify correlates of protection, which is critically important for licensure of new vaccines. We create methods for evaluation and improvement of immunogenicity -- new forms of presentation of antigens to increase the immunogenicity. We, of course, are involved in studies on immunology to study mechanisms of innate and adaptive immunity to understand the response to vaccines and better predict the efficacy of new products. Also, we are involved in studies of adjuvants and the methods to evaluate their potential boosting effect and the best way to use them.

Finally, in the area of availability, we study new approaches to induction of protective immunity, something that could significantly improve immunogenicity of products by delivering it in a different route, using DNA vaccines, modifications of antigen presentation, and so on. We also work on methods to standardize and make the manufacturing process more consistent.

We evaluate new scientific technologies and new platforms for vaccine production, such as plant manufacturing platforms. We also are significantly involved in three R research -- reduction, replacement, and refinement of animal deaths. Finally, we are working on development of new approaches to regulation of probiotic products.

The programs that are submitted by

investigators are evaluated based on three parameters. First is public health significance. Second is scientific merit and qualifications and productivity of investigators. Each project is scored. Based on these scores, the decisions about resource allocations is being made.

Last year, here is the pie chart of our budget. About I would say 40 percent of our resources came from internal FDA budget that was distributed based on this research allocation process that I told you. Some other parts of this chart are also initiatives that are actually run by the Commissioner’s Office. In this case, Critical Path Initiative -- our investigators submit their proposals to the Commissioner’s Office and if they are approved, they are funded directly from the central source.

Modernizing Science is another initiative that was proposed by the FDA. Also, a significant part of our activity last year was pandemic influenza response. So other and royalty -- it should include some grants that our investigators obtained from various sources, such as Department of Defense, NIH, from interagency agreements with other government agencies.

My final slide is, once again, to say that we actually use site visits. We look at site visits as a very important tool in our research management program. First of all, we want to make sure that what our investigators do is really cutting edge science. The first question is whether the program really meets the expectations and is really something that we should be doing.

We also ask site visits to review not only progress, but soundness of scientific plans, what investigators propose to do in the next four years before their next site visit. Finally, there is also an important component of site visit activities to evaluate professional status and professional development of investigators and advise us on some potential personnel actions. I think that this is all I have.

DR. FERRIERI: Thank you, Dr. Chumakov. Are there any questions from the table? Comments? Yes, Dr. Gellin?

DR. GELLIN: I just have one. It is about synergies. You mentioned about some of the work with NIH or maybe other agencies. If you could talk a little bit more about that, regulatory science is the buzz word and how that has changed your scope, and also, synergies with other regulators in other countries since while some of the products are similar, some are different, but some of the challenges are the same.

DR. CHUMAKOV: Thank you. Actually, we have a lot of interactions with other agencies within the US government. National Vaccine Program Office was one of our traditional partners. In the past, the National Vaccine Program Office provided us with significant help at a time when our resource situation was not really good.

We also collaborate with NIH. For the past four years, we have had an interagency agreement with the National Institute of Allergy and Infectious Diseases on some projects. I think there was a total of 12 projects that were initiated on request from NIH. They are increasingly involved in translational research. There are some issues that they need to be addressed that they want to be addressed by somebody who is actually impartial and is professionally suited for the task.

We also have collaborations with the Department of Defense. Recently, we had this meeting with DARPA because they also have some vaccine development and problems and they need us to address some issues that they face.

On our side, of course, we also benefit from these interactions because we have an opportunity to give our input on early phases of vaccine development, way before they reach us in the form of submissions. In some cases, it may be too late to correct the course. I think that this is a mutually beneficial arrangement and, actually, public health wins from these types of interactions.

Regarding our interactions with the international regulatory authorities, we are definitely involved heavily with WHO and other regulatory agencies, such as European agencies and individuals regulatory authorities, such as in England, NIBSC, Paul-Ehrlich-Institut, and so on. We are involved in international efforts to develop new guidances and reference reagents. We participate in their advisory committees. We really are involved in international collaboration.

DR. FERRIERI: I think that will be all then. Thank you very much. We will move on then to the overview of the Division of Bacterial, Parasitic, and Allergenic Products. Dr. Jay Slater will present.

**Agenda Item: Overview of Division of Bacterial, Parasitic, & Allergenic Products (DBPAP), OVRR**

DR. SLATER: Thank you very much. Good morning. The purpose of the three presentations, of which mine is the last, is really to give you sort of the context for this laboratory of bacterial polysaccharides. I am going to give you sort of the closest in context presentation to give you an idea of the immediate regulatory environment and the immediate sort of collegial/academic environment in which LBP operates.

The Division of Bacterial, Parasitic, and Allergenic Products has a name that sounds like it is the product of a merger and, in fact, it is. This is a division that was the merger product in 1999 of the Division of Bacterial Products and the Division of Allergenic Products and Parasitology.

The initial leadership after the merger was under Drusilla Burns. Subsequently, the Division Director was Richard Walker. Finally, Milan Blake was Division Director for two and a half years until he passed away last July and I took over the Division Directorship at that time.

This is the Division structure. The Immediate Office has five individuals, including a Director, Deputy Director, two full time regulatory coordinators. We have a structure of five different laboratories, which I will be going through very, very quickly over the next few minutes. You can see that Laboratory of Bacterial

Polysaccharides is the largest of our units. That is the unit that is the subject of the site visit that you are going to be reviewing.

Our regulatory and research portfolio of organisms and products is represented on this slide, which will be repeated over the next few minutes with different areas colored. The entities that are in parentheses are ones for which there is no product or specific product-related research that goes on, but we do do some research involving these entities, as well. The ones that are not in parentheses are the ones for which there is a specific product that has already been licensed.

The Laboratory of Bacterial Polysaccharides is involved work on invasive organisms, for which the protective responses are to the polysaccharides -- H-flu, Neisseria meningitidis, and strep pneumoniae. They are also responsible for review of the injected version of the Salmonella typhi vaccine, which is predominantly polysaccharide. I am not going to go into any greater detail about LBP because that is the subject of the rest of the morning.

Another laboratory is the Lab of Enteric and Sexually Transmitted Diseases. Broadly speaking, this lab is involved in the regulatory activities for enteric organisms listed here, including the live oral vaccine for Salmonella typhi. This group is also involved in the emerging area of review of probiotics, as well as is part of a division-wide effort to study Staph aureus.

Within LESTD are two principle investigators, Scott Stibitz, who is the Lab Chief, Dennis Kopecko. Their programs are listed here. As you can see, this is a group that has a very active basic microbiologic research going on.

The laboratory of Immunobiochemistry used to be called the Allergenics Laboratory. It reviews allergenic products. It is unfortunate this only covers one line in this table because there are 19 standardized allergenic products and 1,273 non-standardized ones. From a regulatory point of view, this is a very busy laboratory. There are also a lot of investigations going on of novel allergenic products that this lab is responsible for.

In this lab are two PIs, Ron Rabin, who is the Lab Chief, and myself. Again, we have a number of mission-related projects going on within that lab.

The Lab of Mycobacterial Diseases and Cellular Immunology, again, the only product, per se, is PPD, but this is a very active regulatory lab, in part because they have assumed the responsibility for malaria INDs. That keeps them quite busy. They have an active area of interest in Francisella tularensis, as well.

There are three PIs in that laboratory, Karen Elkins, Shelton Morris, who is the Lab Chief, and Siobhan Cowley. Their areas of investigation are listed here. As I indicated, this lab serves as our nexus with the Malaria Program in the Office of Blood. We collaborate with them and have an active program going on.

The second largest lab in our Division is the Lab of Respiratory and Special Pathogens. The main focus of this lab is on non-invasive toxin-producing bacteria, such as listed here. Obviously, for licensed products, their major area of interest is B. anthracis, Bordetella pertussis, Clostridium tetani, and Corynebacterium diphtheriae, but they have interest in other organisms as well. This lab also participates in our division-wide interest in Staph aureus and that is an emerging area of research interest within the lab.

There are five principle investigators in LRSP, Drusilla Burns is the Lab Chief, Juan Arciniega, Eric Keller, Todd Merkel, and Mike Schmitt. Their programs are listed here.

The LBP site visit, which occurred a few months ago involved presentations by all six of the principle investigators, who are listed here. You will be hearing in more detail about LBP.

I just wanted to add my appreciation to what Dr. Wilson said before for the site visit’s work. It involves many hours of preparation, a not inconsiderable amount of travel, a long day in a darkened room, and a lot of hard work and a lot of follow-up afterwards to fine tune the site visit report. We want you to know that we deeply appreciate your efforts and we deeply depend on the product of your work to maintain the quality of our programs. Thank you very much.

DR. FERRIERI: Thank you, Dr. Slater. Questions or comments from the panel, here? I guess not. Thanks again. We will move on then to the overview of the Laboratory of Bacterial Polysaccharides by Dr. Willie Vann.

**Agenda Item: Laboratory of Bacterial Polysaccharides**

DR. VANN: I am going to give you an overview of the Laboratory of Bacterial Polysaccharides. The Laboratory of Bacterial Polysaccharides investigates the biochemistry, biology, chemistry, immunology of virulence factors of encapsulated bacteria. These virulence factors include capsular polysaccharides, lipopolysaccharides, and outer membrane proteins.

These basic research fields are related to the regulatory activities of the Laboratory of Bacteria Polysaccharides, which include review and approval of biological license applications and IND submissions related to polysaccharide and polysaccharide conjugate vaccines, in addition to non-capsular immunogens of encapsulated pathogens.

We have product responsibility for several licensed products related to polysaccharides. These include licensed polysaccharide vaccines and licensed glycoconjugate vaccines. Responsibility include BLA review, review of supplements, inspections, and lot release, to name a few of the responsibilities.

Polysaccharide vaccines include the 23 valent pneumococcal polysaccharide, a quadravalent meningococcal polysaccharide vaccine, the VI polysaccharide vaccine. And there is an ever-growing list of glycoconjugate vaccines -- a quadravalent meningococcal vaccine conjugated to diphtheria toxoid, a quadravalent meningococcal vaccine conjugated to CRM197, the recently licensed 13 valent pneumococcal polysaccharide vaccine conjugated to CRM197. There are two haemophilus polysaccharide vaccines that are conjugated to tetanus toxoid and one that is conjugated to outer membrane protein vesicles.

During this review period, especially in the last two years, the Laboratory of Bacterial Polysaccharides has had quite a bit of regulatory responsibility. Here, listed on this slide, are some of the major regulatory accomplishments.

The first is a second tetravalent meningococcal conjugate vaccine, which we received the submission in the latter part of 2008. It was licensed in February of 2010. There was another haemophilus conjugate vaccine that was licensed in accelerated review. Received in 2009, it was licensed before the end of 2009. The 13 valent pneumococcal conjugate vaccine, which was licensed also in February of 2010. Both of these required an enormous amount of work for a very diverse review team.

The Laboratory of Bacterial Polysaccharides is organized into six sections, under six different PIs. There is a Structural Biology group, headed by Dr. Daron Freedberg, a Vaccine Structure, by Dr. John Cipollo, Cellular Immunology, by Dr. Mustafa Akkoyunlu, a Bacterial Pathogenesis, Dr. Wei Wang, Glycobiology, myself, and Molecular Epidemiology.

This organization chart represents several changes since the last site visit in 2006. Since the last site visit, Dr. John Cipollo was actually hired as a PI in vaccine structure. He is a mass spectrometrist. Dr. Wei Wang is the newest person who was hired. She is a microbiologist. Dr. Margaret Bash, who is a medical officer and clinical reviewer, at the time of the last site visit, was actually a sub-section under Glycobiology. She is now recently been given elevated to a level of a PI. Glycobiology, there are actually two sections. One is biochemistry and the other is conjugation chemistry.

The major areas of research for the Laboratory of Bacterial Polysaccharides are listed in the next two slides. Dr. Mustafa Akkoyunlu, who was the PI for the Cellular Immunology Group, studies the immunobiology of the host response to capsular polysaccharides of encapsulated bacteria. Dr. John Cipollo, head of Vaccine Structure Group, uses mass spectrometry based strategies to investigate the role and significance of glycoconjugates in the infective process.

Dr. Daron Freedberg, head of the structural biology group, is trying to discern the conformational structure of polysaccharide antigens. Dr. Margaret Bash, who you will hear a lot from tomorrow, studies the outer membrane protein diversification as it relates to vaccine safety and efficacy.

Dr. Wei Wang brings new expertise to the laboratory, which is especially relevant to the new types of vaccines that are based on genomics. She studies the genetics of M. catarrhalis. My laboratory, the glycobiology group, has two sections -- one, biochemistry, where we study capsular polysaccharide biosynthesis and new designs of how to make a conjugate and also a conjugation chemistry where we use current methodology to make low cost vaccines for the developing world.

I would like to highlight three of the research programs to highlight some of the recently published work and innovative strategies that are being taken in these groups.

The first is that of Dr. John Cipollo, who studies C. elegans. He uses C. elegans as a surrogate host for glycan-dependent host infection. C. elegans is an interesting organism in that many of the bacteria that infects the elegans also infect humans. Dr. Cipollo is using this organism to ask questions about and using genetics to ask questions about what glycoconjugates are important for infection.

The structural biology group, under Daron Freedberg, is looking at polysaccharides that have been a long-standing problem to us -- and that is understanding the polysialic acids or mening B polysaccharide. He is using High Field NMR techniques to understand the confirmation of this polysaccharide structure. He has found hydrogen bonding in these polysaccharides, which suggest a definite three-dimensional structure.

Dr. Wei Wang, who actually identified a denitrification pathway in M. catarrhalis. That denitrification pathway appears to be important for the virulence of M. catarrhalis. M. catarrhalis is a close cousin of Neisseria. Perhaps such a pathway also plays a pathogenic role in Neisseria.

The Laboratory of Bacterial Polysaccharides has regulatory responsibility for vaccines against encapsulated bacteria and products containing bacterial polysaccharides. The overall goal of the research program of the Laboratory is to understand the virulence factors that are components of vaccines against bacterial pathogens.

The research program of the Laboratory of Bacterial Polysaccharides is directly related to the understanding of the physical, chemical, and immunological properties of bacterial polysaccharides and vaccines against encapsulated bacteria.

The knowledge and expertise gained in this research endeavor provide a scientific basis for our decisions related to the review of manufacturing, purity, potency, and safety of carbohydrate containing vaccines. Thank you.

DR. FERRIERI: Thank you, Dr. Vann. We are at a point in the program where we can have questions and answers from Dr. Vann -- to him and from him, as well as any other question from the Committee members. It applies to anything you have heard that you might have a question now. The questions could be for previous speakers, as well.

People are stunned this morning. I think we need to rev up our metabolism, perhaps. I guess there are no questions for you, Dr. Vann.

Again, the Committee members can ask anything that they have heard about or that might be on their mind about the topic I presentation. If not, then I would ask is there anyone in the audience for the open public hearing, who would like to make a statement or ask any questions? If there is anyone in the audience, then I have to read a statement prior to your speaking.

It appears, for the record, there is no one. We now are at a point where we can take a break. We have to convene then -- I think we should take only a 15 minute break, perhaps. Don, do you have any advice for me? We could take even a 20 minute break, perhaps. We have decided 10:20, please be back at the table. We will be ready to go.

MR. JEHN: That session will be closed so at that point we only need the standing committee at the table. Everybody else is excluded with the exception of the Chair for the site visit.

DR. FERRIERI: Thank you.

(Break.)

(Reconvene in closed session until luncheon recess.)

A F T E R N O O N S E S S I O N

**Agenda Item: Topic 2: Demonstration of Effectiveness of Meningococcal Serogroups A, C, Y and W135 Conjugate Vaccines in Children Younger Than Two Years of Age**

DR. FERRIERI: Good afternoon, everyone. Please take your seats so that we can start on time.

I am Dr. Patricia Ferrieri from the University of Minnesota Medical School. I am the Acting Chair of the meeting today and tomorrow. We will start with Topic 2, demonstration of effectiveness of meningococcal serogroups A, C, Y and W135 conjugate vaccines in children younger than two years of age. Our first speaker of the day is Dr. Lucia Lee, who will give us an introduction and background.

**Agenda Item: Introduction/Background**

DR. LEE: Good morning. My name is Lucia Lee. I am a medical officer at the Food and Drug Administration. I will be presenting today the topic for today's session, an approach to demonstrating effectiveness of meningococcal conjugate vaccines in children younger than two years of age.

This session also serves as a segue to tomorrow's session for vaccines to prevent meningococcal B disease.

Before I begin, I would like to bring attention to some of the terms used in the briefing document. The words correlate, surrogate and biomarker have different implications when interpreted by a clinician, statistician or regulator. Please disregard these terms, as these words weren't intended to be the topic of today's discussion. Instead, to avoid confusion, the general terms immune marker or serologic marker of protection are used in the presentations today.

With that, let's begin. Meningococcal conjugate vaccines intended for use in infants and young children have been studied in clinical trials. License applications and supplements are being prepared or have been submitted for FDA review. The indication is to prevent invasive disease caused by meningococcal serogroups contained in the vaccine.

Effectiveness using a serologic marker of protection, bactericidal antibody, has been an approach used before for licensure of meningococcal conjugate vaccines in older children and adults. For individuals two years of age and older, effectiveness was demonstrated by non-immunologic non-inferiority to a U.S. licensed meningococcal vaccine.

However, in children younger than two years of age, since meningococcal conjugate vaccine has not been licensed in the U.S. for this age group, protection against meningococcal disease would be indicated by the presence of meningococcal specific bactericidal antibodies in the serum, rather than comparison to a vaccine with established effectiveness.

Use of serum bactericidal antibody measurements to infer effectiveness of a meningococcal vaccine in this age group would be based on the viewpoint that circulating antibodies present at the time of exposure protect against meningococcal disease, and that meningococcal conjugate vaccine induced functional antibody can be accurately measured by human complement serum bactericidal activity assay.

The presence of bactericidal antibody by a predefined titer measured by SBA assay can be predictive of protection. Specific titers that have been historically used as indicators of protection will be described in a few of the presentations today. The committee will not be asked to make conclusions about what titer constitutes the protective level, since end points may vary with assay validation. The purpose of today is mainly to describe the approach that in concept, the presence of bactericidal antibody can be predictive of protection.

I would like now to give some background information about meningococcal vaccines licensed in the U.S. to provide some regulatory context for the approach being used today.

Currently there are three meningococcal vaccines that are licensed and available in the U.S. One is a quadrivalent polysaccharide vaccine, MPSV4, and the other two are conjugate vaccines using diphtheria toxoid or CRM as the carrier protein.

All of these vaccines are currently approved for use in children as young as two years of age.

As with any new vaccine, there are requirements for safety and effectiveness. Clinical efficacy studies to support U.S. licensure would be the clearest demonstration of benefit of a vaccine to prevent disease. Alternative methods to children end point studies such as a serologic response evaluation would be adequate to show effectiveness where an association between the antibody responses generated in this way and clinical effectiveness already exist. This was the approach used for meningococcal polysaccharide vaccines.

Meningococcal A and C polysaccharide vaccines were licensed in the 1970s based on children efficacy data. Serogroup C polysaccharide vaccines were based on two randomized controlled field trials which in total enrolled about 28,000 military recruits in the vaccine group and about 114,000 in the control group. Vaccine efficacy from the combined data sets was 89 percent.

For serogroup A polysaccharide vaccines, analysis seven controlled vaccine field trials were conducted. The vaccines were found to be protective in older children and adults and had short term protection in infants.

In 1981 the current quadrivalent vaccine was licensed. Approval was based on immunologic criteria. A vaccine response was defied as a fourfold or greater rise in serum bactericidal antibody achieved in at least 90 percent of adults.

For the A and C components, clinical efficacy data from trials with monovalent and bivalent meningococcal polysaccharide vaccines were available, but for Y and W components, the seroresponses that were comparable to responses to the A and C components were the primary basis for demonstrating effectiveness. Due to the low incidence of serogroup Y and W disease, vaccine effectiveness for these two components was not directly measured in a clinical end point trial.

The use of immunologic markers of protection for approval of new meningococcal conjugate vaccines was discussed at a VRBPAC meeting in September 1999. In brief, the committee concluded that use of immunologic marker protection could be used to demonstrate effectiveness, and the effectiveness of a new vaccine would be acceptable if antibody responses to an investigational meningococcal vaccine was comparable to that of a U.S. licensed meningococcal vaccine.

At the time, MPSV4 was the only U.S. licensed vaccine available. The lower age limit for use of this vaccine was two years old.

For the two quadrivalent conjugate vaccines, effectiveness was inferred using this approach by demonstrating immunologic non-inferiority to a U.S. licensed vaccine. Since the polysaccharide vaccine was approved in children two years of age and older, the lower age limit of the two conjugate vaccines using this approach was also limited to children two years of age. Initial licensure of those vaccines for individuals 11 to

55 years old was based on an assay that included a human component source, and subsequently used for children two to ten years old, also used an assay with a human component source.

The demonstration of meningococcal conjugate vaccines in children younger than two years of age is based on the same principles. If a clinical efficacy trial in this age group is not feasible, then an alternative approach would be possible if the serologic marker in this age group represented a biologically relevant marker of protection, and that the assay could reliably measure antibodies that were protective.

I will now briefly review today's agenda for this discussion. Dr. Amanda Cohn will describe the epidemiology of meningococcal disease in the U.S. and results from a postlicensure surveillance study. Dr. Wendell Zollinger will present information about bactericidal antibodies measured by an hSBA assay as an indicator of vaccine effectiveness, and then my presentation will place things into a regulatory perspective for committee concurrence of this approach and any advice regarding any additional information that might be needed.

DR. FERRIERI: Thank you, Dr. Lee. We will move on then to Dr. Cohn's presentation. This is the epidemiology of meninge in the U.S.

**Agenda Item: Epidemiology of Meningococcal Disease in the U.S.**

DR. COHN: Good afternoon, and thank you for having me. Today I will be presenting an overview of the epidemiology and burden of meningococcal disease in infants and young children, focusing specifically on serogroups C and Y, as well as the preliminary vaccine effectiveness results of men ACWY or meningococcal conjugate vaccines in adolescents.

Meningococcal disease affects all age groups. However, there is a high proportion of disease in young infants and adolescents. There is a high case fatality ratio, and there is substantial morbidity among survivors of meningococcal disease. An adolescent vaccination program which has been implemented for the last several years may be informative to questions around infant vaccination.

The initial ACIP recommendations for meningococcal conjugate vaccines were in 2005, with the preferred age being ages 11 and 12. In January 2011 a booster dose was recommended at age 16.

We have two data sources that provide information on meningococcal disease incidence and epidemiology. The first is active bacterial core surveillance system or ABCs. ABCs is an active laboratory and population-based surveillance system that operates in ten states in the U.S. and covers approximately 13 percent of the population. ABCs conducts surveillance for six invasive bacterial pathogens including *Neisseria meningitidis*.

The National Notifiable Diseases Surveillance system also collects information on meningococcal disease. NNDSS is a passive surveillance system and all states and territories report data for all nationally notifiable diseases. Both of these systems provide valuable information that will be used today.

Finally, we will also be using published reports of sequelae and estimates of severity.

This graph shows the incidence of meningococcal disease in the United States from 1970 to 2008. Historically meningococcal disease has been cyclical, with peaks in disease incidence every eight to ten years. However, rates of disease have been declining for the last ten to 15 years, and we are currently at a nadir of disease incidence in the United States. It is not known why disease incidence has continued to remain low, but it is unlikely to be due to the introduction of men CV4, since most of the decline occurred prior to 2005 and coverage in the first couple of years of implementation was low.

This slides shows rates of disease by serogroup over the last decade. Again, we see that rates of disease have been declining and this decline has been observed in all serogroups including serogroup B, which further supports that meningococcal conjugate vaccine is not responsible for this entire decrease in disease incidence.

This slide shows incidence in meningococcal disease by age. Disease incidence is highest in infants and children less than five years of age. However, there is also a peak of incidence among adolescents and again in older adults.

This slide turns incidence into estimates of average annual number of cases by single year of life. The number of cases in children aged less than one year is substantially higher than any other single age year of life, and the number of cases in one and two-year-olds is very similar to the number of cases that occur in adolescents. However, a larger portion of disease caused in young children is caused by serogroup B compared to adolescents.

This slide looks specifically at children aged less than five years. We see that the greatest incidence in this age group is among children aged less than one year. Additionally, 50 to 60 percent of disease is caused by serogroup B and 30 percent of disease in less than one-year-olds is caused by serogroup Y.

This slide breaks down the number of cases in less than five-year-olds into serogroup and into smaller age groups. In the first eight months of life serogroup Y causes the majority of serogroup C and Y disease in young children, but then in one year and older serogroup C causes more disease. Also, the incidence of disease is substantially higher in children less than eight months of age compared to children nine months of age to five years.

This slide uses NNDSS for annual number of cases, but estimates the proportion of disease that is vaccine preventable using ABC's data. The number of cases in children ages six to 59 months has halved since the year 2000.

This slide compares the number of cases in infants and young children to cases in adolescents. The absolute number of cases is similar in both adolescents and young children. However, the proportion of disease caused by serogroup C and Y is much higher in adolescents, so the estimated cases of serogroup C and Y is higher in adolescents compared to infants. As a comparison, the cases in ABCs is given. This number is a ten-year average annual incidence, which is higher than the NNDSS average over the last four years.

I am now going to move on to discuss morbidity and mortality of meningococcal disease in the U.S. This slides shows hospitalizations of meningococcal disease from 1999 to 2008. Ninety-two percent of all cases of meningococcal disease are hospitalized, and many of the unhospitalized cases actually die before presenting to the hospital at all, so close to 99 percent of cases that survive are hospitalized.

The median length of hospitalization is about seven days for infants less than one year and six days for all other age groups. The range varies but the median is the same. And hospitalization does not vary by month of age, serogroup or syndrome.

This slides shows meningococcal cases in children less than two years of age by serogroup and syndrome. For serogroup C, 62 percent of cases cause meningitis, whereas for serogroup Y 44 percent of cases cause meningitis and 17 percent are in this other category, which consists of pneumonia and septic joints, for the most part.

This study is from a multi-center study of pediatric meningococcal disease in the United States from 2001 to 2005. Children ages less than five years of age were less likely to require mechanical ventilation but were more likely to have hypertension. These children were also less likely to have purpura and to die as a result of the disease.

This slide shows updated information from the same study with certain sequelae broken down by serogroup. If you look at children age less than five years, necrosis is more commonly seen in serogroup C or Y cases, with hearing loss fairly equally distributed. A higher case fatality ratio was seen in serogroup B cases. However, outcome information was reported for fewer of the serogroup C and Y cases.

This slide shows data from Quebec, Canada from 1990 to 1994, and it is specific only for serogroup C disease. What we see here is that major complications including death, which are shown by the solid black bars, are more prevalent in older age group, whereas minor complications, shown in the open bars, -- I'm sorry, the deaths are shown in the hatched bars -- are fairly similar amongst all of the age groups.

Finally I want to touch briefly on long term neurologic sequelae associated with all-cause bacterial meningitis. We don't have very good data on long term outcomes in meningococcal disease in young children and infants, but we can make some inferences from studies that have been done on all-cause bacterial meningitis.

Long term neurologic sequelae are difficult to measure. However, more than two-thirds of young children with all-cause meningitis exhibit neurologic or neuropsychological deficits after acute bacterial meningitis, and nearly one-fifth of children with meningitis have a permanent severe or moderate severe disability and subtle deficits are also more prevalent.

This slides shows average annual deaths and case fatality ratios by serogroup and age. Young children less than aged two years are less likely to die from meningococcal disease compared to older age groups. Also, serogroup C has a higher case fatality ratio in the less than two-year-old age group compared to serogroup B which is second, and serogroup Y, which is fairly low.

In summary, while infants aged less than one year are at greater risk for meningococcal disease, the amount of potentially preventable disease in infants is low. We are currently at a nadir in disease incidence. There is a low proportion of serogroup C and Y disease and there is declining incidence after the first six to eight months of life. Additionally, morbidity and mortality in infants is lower than in other age groups.

Now I am going to move on to present preliminary results of a vaccine effectiveness study that is currently underway. While there are currently two meningococcal conjugate vaccines licensed, the results of this effectiveness study focus on Minactra, since it has been licensed for several more years than the second vaccine.

These results are from a case control study. Enrollment has been ongoing since January 2006 and is currently being conducted in 29 health departments. We use provider verified vaccination records. A case of meningococcal disease was considered to be confirmed if *Neisseria meningitidis* serogroups A, C, W or Y was isolated from a normally sterile site or with detection by PCR. So while ABCs does not include PCR positive cases, this case control study did.

I want to point out that there have been challenges due to the low disease incidence and the difficulty enrolling adolescents in this age group, which are part of the reasons why this study has taken awhile to conduct. The cases are matched by age and state and were friends and school controls.

The analysis was done using traditional logistic regression, controlling for underlying illness and smoking, and vaccine effectiveness is one minus the odds ratio.

This slide shows cases by serogroup and vaccination status. We currently have 120 cases enrolled in total. This slide breaks down into serogroup C and Y and serogroup W135. The point of this slide is to show you that we have 54 serogroup C cases enrolled, 40 Y and only five W135, and for controls we have 100 controls enrolled for serogroup C and 62 enrolled for serogroup Y. I want to point this out because our serogroup specific estimates which are an important part of this study, we feel more comfortable presenting for serogroup C as opposed to the other serogroups because we have a greater number of cases and controls enrolled so our estimates are more stable.

This slide shows the demographics of the eligible cases, the enrolled cases and the controls. There are some differences between the enrolled cases and controls. There were more male enrolled cases compared to controls, and there were more black enrolled cases compared to controls, but we have not teased out how these differences might impact the analysis.

The case fatality ratio in eligible cases was 13 percent and enrolled cases was ten percent, so there were some deaths. There was some bias towards not being able to enroll cases where the case died.

This slide shows the proportion of cases and controls vaccinated with Menactra by year. This starts in 2006 when vaccine coverage was very low and was less than ten percent in both cases and controls. In 2007 it increased in the control population to about 20 percent. In 2008 it was over 50 percent. It came back down in 2009 and then increased again in 2010.

I just want to point out that the differences in vaccination coverage by year are likely due to where the cases were enrolled from. Vaccination coverage in the U.S. right now is highly variable, depending on the state. It ranges from 18 percent to 80 percent. So that is likely the differences between 2009 and 2010.

Our preliminary estimates for vaccine effectiveness for Menactra in the first five years after vaccination, for serogroups C, Y and W135 combined are 74 percent. That confidence interval is 35 to 90 percent.

Our serogroup C specific estimate is 83 percent with a confidence interval of 38 to 95 percent.

This slide shows our preliminary Menactra vaccine effectiveness estimates, but includes a look at duration of protection. The first column shows vaccine effectiveness for all cases, which includes controls but includes cases with underlying illness. The second column is vaccine effectiveness for cases with no underlying illness. So vaccinated less than one year, it is 99 percent for both groups, vaccinated one to two years, it falls to 80 percent in the group that includes persons with underlying illness, and increases to 89 percent in just healthy adolescents.

For vaccinated two to five years, our vaccine effectiveness falls to 46 percent in all cases, increases to 56 percent for healthy adolescents. Notice that that point estimate is 56 percent, but the confidence intervals for two to five years post vaccination are fairly wide; it is negative 48 to 87 percent. While these confidence intervals have tightened since the last analysis which was about six months ago, the point estimate has remained the same.

Since we implemented conjugate vaccines in 2005, our understanding of how we are protected against meningococcal disease is evolving. We now understand that immunologic memory is not enough.

This comes from data from the United Kingdom for their men C vaccine. The boost response takes five to seven days after exposure, but the incubation period of *Neisseria meningitidis* is just one to four days. So the rapidity with which *Neisseria meningitidis* invades is in part responsible for not allowing the memory response to play as large of a role in protection as we would normally expect with conjugate vaccines.

Secondly, vaccine failures occur in persons in whom immunologic memory can be demonstrated. In the United Kingdom they demonstrated that there was a boost response in persons with meningococcal disease that indicated that they were primed prior, but they did not respond rapidly enough to prevent them from getting disease.

Additionally we are unlikely getting the additional benefits of herd immunity with the current U.S. program. While our coverage is increasing slowly, it is currently only about 60 percent. While our overall coverage of 60 percent, adolescent immunity at the population level is likely lower than 60 percent because ten percent of those adolescents were vaccinated five years ago and 20 percent were vaccinated four years ago, so as peoples' immunity wanes over time, we don't have this entire population of vaccinated persons contributing to this herd immunity effect.

The third bullet point is that we need circulating antibody at the time of exposure for protection.

This slide shows Menactra serum bactericidal antibody. This is the percent of subjects with greater than 1 to 128 post vaccination for serogroup C. The reason why I am showing this slide is to show you the declining levels of antibody one month, three years and five years post vaccination. Five years post vaccination the proportion of vaccinated persons with baby rabbit SBA greater than 128 is about 54 percent.

Notice, because I will come back to this in a minute, that in our age-matched naive persons in this study, the proportion with bactericidal antibodies greater than 1 to 128 is also above 40 percent.

This is similar data with Menveo and Menactra in a percentage of subjects with human SBA greater than one to eight for serogroup C. I just want to point out that these antibodies for both vaccines wane between one month and 22 months to about 60 percent, and are very similar 36 months after vaccination compared to 22 months. But we don't have five years out from this prelicensure study.

The question is, does our observational effectiveness inform our interpretation of serologic data. I pulled back this slide where we see five years after vaccination you have 54 percent over this one to 128 titer in vaccinated persons compared to 42 percent in the unvaccinated persons. The vaccine effectiveness estimate that we have two to five years after vaccination is also 55 percent. But I want to point out that our vaccine effectiveness estimates are not just a number of people who are protected in total, but incorporate the level of protection in the unvaccinated cohort as well.

So our vaccine effectiveness is one minus the attack rate in the vaccinated over the attack rate in the unvaccinated. So if there is some level of protection in the unvaccinated, that is being incorporated into our vaccine effectiveness. So it is the amount that the vaccine is effective compared to the unvaccinated, which is not the same as the 54 percent that have an SBA titer of greater than 128 as you see in this slide.

So the serologic markers of protection do not incorporate natural protection in the unvaccinated, so vaccine effectiveness is not directly inferred from serologic markers. While the trends are very similar, you can't say that 55 percent from our observational vaccine effectiveness is the same as the 55 percent that you are seeing in this data.

In summary, trends in observational data and serologic data are consistent and indicate waning immunity. And serologic markers of protection should be correlated with postlicensure clinical efficacy.

Thank you.

DR. FERRIERI: Thank you very much, Dr. Cohn. We will move on then with the next presentation by Dr. Wendell Zollinger, who is a consultant for meningococcal vaccines, on the measurement of serum bactericidal antibodies, an indicator of vaccine effectiveness.

**Agenda Item: Measurement of Serum Bactericidal Antibody as an Indicator of Vaccine Effectiveness**

DR. ZOLLINGER: Good afternoon. My assignment is to speak about the bactericidal assay itself and how it can be used as a reliable biological marker for predicting vaccine efficacy.

We are well aware by now that the serum bactericidal antibody is probably the best biological marker we have predicting vaccine efficacy for meningococcal vaccines. There is quite a bit of data that supports that conclusion, which I won't discuss but will be discussed by Dr. Lee and others in later talks.

I want to focus on the idea that a serologic marker of protection ought to be a marker that is a measure of the biological function that is associated with immunity, and can substitute for a clinical end point such as vaccine efficacy.

The bactericidal assay itself is not very complex. There are four components that we put together and incubate for an hour and then see what happens. Serial twofold dilutions of the sera to be tested are usually made using a chosen buffer or diluent, then log phased viable bacteria are added and then a source of component, usually serum or plasma without intrinsic bactericidal activity. The mixture is incubated for 30 to 60 minutes and then the viability of the organism is determined by one means or another.

Not every antibody that is induced by a vaccine is bactericidal. Some isotypes of antibody have more activity or support bactericidal function better than others, IgG-3 being probably the best. IgM can support bactericidal activity with a single molecule, whereas for the IgG it is necessary to fix two molecules of IgG quite close together to fix component and result in bacterial lysis.

It is now clear that these two antibodies can either be on the same molecule or they can be attached to different antigens that are situated close together in the membrane. So you can get cooperative effects from antibodies against different antigens or different parts of the same antigen.

Before going into the assay itself, I wanted to spend just a minute to look at the question of what level of bactericidal antibody is sufficient to provide protection. That has been discussed a lot. I won't give you a final answer to that, but I think it is important to consider briefly what we know about it.

The classical work of Goldschneider, Gotschlich and Arnstein used a titer of one to four to determine if a person was protected or not. Others have more recently suggested maybe a titer of one to eight would give a little more margin of safety as an end point for that prediction. The end point is usually taken as that dilution at which at least 50 percent of the bacteria are killed.

There have been a couple of studies that have explored the question, trying to look at what titer corresponds to protection. The first of these was done using a group B vaccine, the outer membrane vesicle vaccine produced in Norway at NIPH. Johan Holzt and others published this graph that shows a super position of two studies. The first was their large efficacy study in which they plotted on a graph.

These two plots here show the accumulative incidence of disease cases in the placebo or unvaccinated population and the vaccinated population. Then in a subsequent study where there were three doses given rather than two doses, they measured the geometric mean titer of bactericidal activity as a function of time. They found in superimposing these curves that at this point where the vaccine appeared to have been losing effectiveness and more cases began to appear in the vaccinated population, was where the antibody level had dropped to approximately one to four titer.
So that is a broad population-based result, but it is interesting that it could come out in that manner.

The other study I wanted to mention is more recent, published by Andrews and others. It is based on the studies in the U.K. This study was done in conjunction with the mass vaccinations with the C conjugate vaccine in the U.K. They used in these studies a baby rabbit component instead of human component. They showed that when plotting the number of individuals one month after vaccination with the conjugate vaccine, the number of individuals with titers equal to or greater than these titers indicated below. Up here they indicated the level of vaccine efficacy that they observed in the field, which is about 90 percent.

They found that those who had titers of greater than or equal to one to eight, there were 90 percent of them that had that titer, so that matched up pretty well. However, there is a pretty broad confidence interval, 95 percent confidence interval, so it could have been a level even higher than that required, but these are interesting attempts to try and see how much bactericidal antibody might be required for protection.

If you look at the assay itself, in order to have a reliable assay predicting potential efficacy of a vaccine the assay needs to be reproducible. Ideally it would be standardized and be able to be portable from one lab to another, and one that you could rely on for results.

There are three major sources of variables that need to be controlled in order to have a reliable assay. The choice and management of the test strain is a very important variable. We will talk more about each of these. The source of component, the amount of complement used, and the various other parameters in the assay.

Some of these parameters that we need to pay attention to include the way the test strain that is chosen is grown and handled prior to putting the organisms in the assay, source and concentration of complement, the growth media and diluent composition, incubation time and conditions, method of determining the cell viability after the incubation time, and the definition of the end point titer.

These things really need to be standardized if the assay is going to be comparable lab to lab. Dr. Ray Borrow in the U.K. has done assays for a lot of people and a lot of companies, and has developed a pretty standardized assay which has allowed some comparability between companies. But in various other labs the assay is done differently.

Here I have listed some of the parameters that might vary and some of the different conditions that are used in different laboratories. This is not all the conditions, but just three or four of the laboratories that I am familiar with.

So for the initial setup of cells, we might use Columbia blood agar with five percent sheep or horse serum added blood. Some use Mueller-Hinton agar, some gonococcal agar with a defined supplement.

The inoculum is important. Some people have used a single colony from the initial setup to expand and put into the assay, and others have proposed using a larger number, eight or ten colonies, and others a suite, or many, many colonies to expand for the cell population that is used in the study. I will come back to some data with regard to this. It turns out that using a lot of colonies is a better way to go than working from a single colony in terms of reproducibility.

In terms of growing up cells for the assay, some of the laboratories do a stretched streak and grow for four or five hours on agar plants and take the cells right off the plate and dilute them up for the assay. Others grow the cells in Mueller-Hinton liquid medium or Mueller-Hinton medium with added glucose and/or CMP-NANA to insure cyalation or full encapsulation.

Incubation conditions usually are 36, 37 degrees for either 30 or 60 minutes. But sometimes the plate is just left static for that period of time, others maybe tap it every so often to make sure it is mixed. Others have it on the rocking shaker, and others on a microplate shaker that shakes rather rapidly. So there is a lot of variation in how the plate is handled during the incubation period.

The diluents typically are a buffered salt solution, either Hanks. Different amounts of BSA are added to the solution to stabilize the organisms. Dulbecco's PBS with calcium and magnesium has been used, and Gays balanced salt solution with a protein, BSA or gelatin is used in different laboratories.

The number of cells put into the test. A low number of cells are typically used if the agar overlay method of counting the cells is to be used, where they put agar right into the microplate wells and let them grow in place. You can only count so many colonies in a small microtiter well. Then up to $10_4$ or $10_5$ cells per ml when the tilt plate method where the organisms are plated out and then counted the next day on the surface of the agar.

Complement is important. There is variation between ten and 25 percent human serum or baby rabbit complement.

The serum is usually heat inactivated, sometimes not. Viability determination, either plate on agar by a tilt or drizzle method are overlaid in microplate wells.

So there are a lot of variables, a lot of things that can vary. Some are more important than others obviously, but ideally these would all be controlled and done the same way for reproducible and standardized assays.

Say a little bit more about the complement source. As I mentioned before, the studies of Goldschneider linking bactericidal antibody with protection were done using human complement, with intrinsic complement that is sera well saved to preserve the complement in the individual's own serum.

The bactericidal assay with human complement is the best serologic marker of protection. It is most consistent with what happens in vivo as a means of protection against disease in a human being.

Baby rabbit complement may be more convenient and easier to standardize, but it does give significantly different results. It not only uses generally quite a bit higher titers, but that is not the only issue. There are more complex issues than that that make it different.

There are certainly some species specific differences. For example, factor H-binding protein expressed by most meningococci does not bind rabbit factor

H, where it does human factor H, which can inhibit the bactericidal effect.

Also, rabbit complement appears to function with somewhat lower avidity antibodies. I think this can make a big difference as well. We originally determined the importance of the complement source when we found that antibodies against the group B capsular polysaccharide found in normal human sera or following vaccination were generally IgM and of low avidity. They were quite bactericidal with rabbit complement, but with human complement they were not bactericidal. So this is another reason particularly for group B vaccines that is important to use human complement.

Some efforts have been made to correlate rabbit complement assay with the human assay. This can be done to some extent, trying to compare different cutoff titers. But there are population-based comparisons. I think the rabbit complement assay is much less reliable for predicting protection in any given individual. We ought to stick to the human bactericidal assay.

Two other points. When we use human complement, we have complement from different individuals which may have slight differences in its activity and maybe other antibodies and things that might be in there. That can be a problem and needs to be controlled.

One way to partially control that is to make pools of serum so that you are averaging out in the effects that might be present in an individual source of complement, and thereby make things more equal.

It is also a good idea for each batch of complement to measure the complement activity of the C' H-50 assay or something and qualify each complement lot as having sufficient activity to fall between a particular range.

To look a little bit at the considerations of choice of a target strain for use in the assay. Target strains can vary considerably to how sensitive they are to killing by the same serum, same set of sera. There may be differences in the thickness of the amount of capsule on the organism. There may be differences in the amount of factor H-binding proteins as expressed or in the type of LOS that is expressed, whether it is cyalated or whether it is short or long, can affect the sensitivity of the organism.

So it is a good idea to thoroughly characterize test strains to know what is being expressed and compare them with other strains to make a good choice that would represent the average strain out there for the groups A, C, Y and W where there are not as many problems as for B in choosing the strain. But still, I think it is important. If you look at a lot of group B strains, for example, you may find some that you can hardly kill at all and others that are killed quite easily. So we need to have one that is representative of most case isolates.

Some important antigens to monitor. I think one good way of monitoring looking at this question is to do colony blots, maybe with monoclonal antibodies, where you can see what is being expressed by the whole population. Maybe antigens subject to phase variation are half turned on, half turned off. Opc is one like that, where typically it is undergoing quite rapid phase variation. You may have some percentage of the cells expressing this protein and others not. Factor H and others, LOS undergoes phase variation also. It is a good idea to use a strain that expresses a full length LOS that is typical of case isolates.

This table is taken from a paper coming from our lab at Walter Reed some years ago, where we compared the relative sensitivity of three phase variants. These are group B strains that express different types of LOS, either the full length L37 or mixture of the L37 and the L8 or the shorter L8 LBS.

We had three different serum pools from either mouse serum or two human serum pools. In one case we had absorbed it with PorA deficient strain in order to remove antibodies against everything but PorA. So we are trying to make sure this effect was not just due to antibodies to the LOS.

In each case these are log two results. It is about two or three dilutions higher titer obtained with the LH strain than with the L37. So this is just a good idea to control the strains with regard to LOS expression as well as some of these other factors.

The growth of the cells from the initial setup for the assay, it is good to use a suite or many cells rather than a single cell for the obvious reason that a single cell, if there is phase variation going on in the population, one time you might pick one that is expressing antigen X and the next time you might not. Since there are quite a few antigens subject to phase variation, it increases the variability of the assay to use expansion from a single cell rather than a large number of cells.

For group B, the issues are more complex and probably a panel of strains will be needed for the assay.

That panel may have to differ depending on what is in the vaccine for it to be most appropriate. That will probably be discussed in more detail tomorrow.

For the capsular polysaccharide vaccine, only a single strain is needed for each serogroup. But as mentioned before, it should be well characterized and chosen to be representative of the case isolates from that serogroup.

The impact of two of the parameters that I have mentioned on the outcome of a bactericidal assay were investigated by Ray Borrow and others in a study published in 2005. These two variables were one, whether the plate was left static, just sitting during the incubation period, or whether it was mixed with a raking or rocking action.

The other variable was whether the cells for the assay were grown up from a single colony or from a mixed population of cells. These numbers represent the differences in number of twofold dilutions that were observed with the raking mixture as compared to the stationary, the raking minus the stationary and this one, the single colony minus the -- I've got that wrong, mixed population minus the single colony results.

So either one to two additional twofold dilutions in titer were observed with raking or mixing action versus stationary and with a mixed population versus a single colony. Then they did their standardization comparative study again, controlling these variables, and got much better results. I will show their results in a few minutes.

There has been some work done on trying to standardize the bactericidal assay. These references mostly have to do with the assay for the group B, but I know work has been done by companies who have licensed these ACYW polysaccharide vaccines, which is necessary to have a reliable validated assay for measuring the bactericidal activity.

One of the studies by Ray Borrow and others relates to the data I was just discussing on the earlier slide. They had four different labs participate in an inter-laboratory comparison. In this first study they gave everyone the same strain to work with, the same complement pool or source and the same sera, group of sera to work with. Then they asked how many of these sera will have a titer of one to four or greater. They found that in this first study there is quite a bit of variation, anywhere from ten percent up to 90 percent of the pre vaccination and 42 percent to 100 percent in the post third dose.

So there was quite a bit of variation from lab to lab, even though they had standardized three of the main items in the assay.

Then they further standardized it, correcting the problems with a single colony or many colonies and with the shaking or not shaking of the culture and perhaps a few other things. But once they had a sufficient number of the parameters standardized they got quite good reproducibility between these four different laboratories. So I think it emphasizes the point that you can do it, but you have to control quite a lot of the variables, not just one or two of them, and have the assay really under control.

In conclusion, I would just say that the human complement mediated bactericidal activity is the best biological marker of protection and most relevant to individual protection and the assessment of vaccine immunogenecity. The SBA measures functional antibodies that have been shown to be important in protection from systemic disease, so it is a measure of function activity of the antibodies, which is important.

Standardization is needed. Validation of an assay may not be possible to standardize against all labs, but I think as we can move toward a standardized assay that everyone uses, we will have more data that is comparable from laboratory to laboratory, and it is more meaningful.

So the critical variables are choice and management of the target strain is important, and good agreement can be obtained if there is sufficient standardization of the assay.

Thank you.

DR. FERRIERI: Thank you very much, Dr. Zollinger. That was really an excellent overview of this very important study that is critical in our assessment of immunogenecity with these meningococcal vaccines.

I did have a quick question for you, if you don't mind. Do you remember, in the Borrow study there was standardization of complement inactivation of all the study sera? For example, the post vaccination. My take is that it is advantageous to eliminate intrinsic complement activity. You have a level playing field. What is your preference?

DR. ZOLLINGER: I think it was done in those studies. I mentioned the other option, because we hadn't done that in our laboratory. The intrinsic complement that is remaining in the sera is typically diluted out very rapidly. Sometime IgM antibodies can be inactivated with heat inactivation.

But for the purposes of validating a vaccine or you need really good reproducibility, I definitely support the heat inactivation of the sera.

DR. FERRIERI: Are there any other members of the committee -- yes, Dr. Durbin.

DR. DURBIN: I wondered in the Borrow study as well. After standardization of the assays there was I would say good agreement in terms of the percentages of vaccinees that had a titer greater than four. Was there agreement in the GBT? In the standardization were labs getting similar geometric mean titers from lab to lab, or just they could say the titer was greater than four?

DR. ZOLLINGER: In this paper, as I recall, actually they did look at geometric mean titers. I didn't show those data, but they got pretty good -- after they standardized the assay they did get pretty good comparability on that factor as well in geometric mean titers, yes.

DR. SCHOOLNIK: I have a couple of questions. Is it important to distinguish bactericidal titers that arise from natural bactericidal antibodies that accrue as one aegis versus those that are vaccine induced? If so, how do you make that distinction?

DR. ZOLLINGER: I don't know how you would distinguish between those antibodies that were induced by natural infection versus those vaccine induced. They maybe have different specificities. We looked at some sera, quite a few normal sera and convalescent sera with group B strains. We used an assay we call bactericidal depletion assay, where we try to remove specific antibodies by adsorption to solid phase antigen, different antigens, and see how it affects the bactericidal activity.

So we found a lot of the cross reactive antibodies were against the LOS, whereas in vaccination you get proteins that are polysaccharide or something else. We used some group C case sera, convalescent sera, against group B strains, so the capsule antibody was not a factor in these tests.

I think you just have to look at them separately. I don't know that there should be any difference in levels of bactericidal antibody that would be required for protection, whether it is induced by natural infection or induced by vaccine, as long as it persists long enough to be a valuable antibody.

DR. DURBIN: Thanks. I have one more question, if I could.

DR. FERRIERI: Yes, please.

DR. DURBIN: You discussed the significance of phase variation. I don't want to go too far afield, but has anyone assessed the expression of the critical components of the microbe on the nasopharynx versus in the bloodstream, in order to identify shall we say the phase variation profile that would be most significant to replicate in vitro in an assay that measures bactericidal antibodies, the correlates of protection, if you see what I mean?

DR. ZOLLINGER: I think it is known that one of the ways the organism uses the phase variation is that different antigens or structures may be expressed at different stages during the pathogenic process. So in the throat strains tend to turn off capsule also by phase variation, because it interferes with colonization. But it is essential normally for invasion.

Other structures that involve adhesion, a lot of the adhesion and related molecules are subject to phase variation and can turn on and off. So they might be good targets for bactericidal activity, but essential for adhering to and penetrating through mucosal surfaces.

I don't know that anyone has tried to set up a profile to match for the bug that is invaded. Certainly capsule is one that ought to be there, but there may be others.

I need to be corrected if I am wrong, but I think the organism when it is under stress turns down the DNA repair process by some genes, so that more mistakes occur in replication. Then this leads to the phase variation not being -- a lot of times the phase variation is caused by repeat polymers where such strand sparing occurs, so a mistake is made. If it is not repaired, it leads to some option the organism has. It might be good or bad if it is random, but those that have a good outcome are selected for, they can grow up.

So I think all of those things that have been correlated with pathogenicity, with virulence of the organism, would probably be good things. That is probably what the organism tends to express in vivo, and it would be good to have it on the test organism in the assay so you can kill the rugged organism that is invading.

DR. DURBIN: Thanks so much.

DR. FERRIERI: Your first question, Dr. Schoolnik, is a very intriguing one. Although I can't disagree with Dr. Zollinger's answer about the titers that might be induced and how you would distinguish natural infection from vaccine induced bactericidal activity, I can't help but think that the exposure of the antigen in vivo in a person may be very different. The organism is going to present itself quite differently in toto, and the immune response could be extraordinarily diverse. It is possible that our memory B cells, the repertoire of memory B cells could be very different from my naive perspective.

So I don't know that we have a good answer to that. Dr. Apicella, you had your hand up. This will be our last point and question.

DR. APICELLA: Very nice talk, Wendell. Do you think it would be a good thing, or it would be too much work to make phased lot strains, which can be done, so they are phase on, and use those as standards for vaccine evaluation?

DR. ZOLLINGER: I think that could be a worthwhile thing to do. We have done that a couple of times with Opc, for example, stabilized the expression, so it is not subject to phase variation. I'm not familiar with some of the others, the Opa proteins for example, they could be probably -- choosing alternative codons you could probably stabilize and break up those stretches that turn those on and off and so on.

I think it is a good suggestion. Once a strain is decided on and some of that was done and that could be shared. And not everyone would have to do that.

DR. FERRIERI: Dr. Apicella, do you have any other comments on the presentation otherwise, or any of the requirements, et cetera for the assay?

DR. APICELLA: No. I agree with a major point that Wendell made about use of human complement and making large pools, that we standardize, and standardize before we test them. But I think the rabbit complement is confusing things at times.

DR. FERRIERI: Thank you. I have found that working with baby rabbit complement sources that despite their not having allegedly any antibodies, that it does mess up assays, because they do have something that they interfere.

This has been a very good discussion. We will move on to the last presentation, an approach to demonstrate meningococcal conjugate vaccines effectiveness in children less than two years of age by Dr. Lee again.

She is going to present now the two discussion points for the committee, and then she will give the new talk.

**Agenda Item: Presentation of Discussion Points**

DR. LEE: I would like to present these points which the committee will be discussing today. Please keep these points in mind when listening to the presentations. The discussion points will be restated after the break.

Number one. Please comment on the use of hSBA as an immune measure to infer effectiveness of meningococcal conjugate vaccines for children younger than two years old. Two, please discuss any postlicensure studies that might be needed to further evaluate the effectiveness of meningococcal conjugate vaccines in children younger than two years old.

**Agenda Item: An Approach to Demonstrate Meningococcal Conjugate Vaccine Effectiveness in Children Less Than Two Years of Age**

DR. LEE: You heard presentations by Drs. Cohn and Zollinger. Now I would like to put into perspective the regulatory approach used to demonstrate effectiveness.

Why are meningococcal conjugate vaccines for infants and young children important? *Neisseria meningitidis* is a leading cause of bacterial meningitis, especially in young children. In the U.S., the disease due to serogroups C, Y and W could be preventable by meningococcal conjugate vaccination.

The clinical manifestations of invasive meningococcal disease most commonly present as meningitis and/or sepsis. The onset of illness is often sudden and with rapid disease progression. In individuals who develop fulminant meningococcemia, the progression of disease can occur rapidly and is often fatal within 24 hours from the onset of symptoms. A timely diagnosis is difficult. Even with available treatments, case fatality rates range from ten to 14 percent and up to 20 percent of individuals can experience sequelae.

Meningococci which cause disease is usually encapsulated. These organisms are classified into serogroups based on the biochemical composition of the polysaccharide capsule.

Six serogroups cause invasive disease and five of the six serogroups are serogroups of interest for vaccine development. Unlike meningococcal group B polysaccharide, capsular polysaccharide, A, C, Y and W135 capsular polysaccharides are immunogenic, and anti-capsular antibodies directed against the capsule have shown to be effective. Clinical end point trials would be difficult to conduct in the U.S. due to the low incidence due to the low incidence of disease.

Use of bactericidal antibody to infer effectiveness in children younger than two years of age is supported by the following. Complemented mediated bactericidal activity is the predominant mechanism of protection from invasive meningococcal disease. Although other mechanisms may contribute to protection, complement mediated bactericidal killing is the most relevant to individual protection and for assessing vaccine immunogenecity.

Individuals who have circulating meningococcal specific functional antibodies present at the time of exposure are protected from disease. Serum bactericidal activity with human complement is consistent with an in vivo mechanism of protection. Postlicensure data and studies of polysaccharide and polysaccharide conjugate vaccines have shown that bactericidal antibodies directed against the capsule are effective in disease prevention.

So all factors taken into consideration, the presence of functional antibodies that are bactericidal measured by an hSBA assay can be predictive of protection.

I would like now to describe the complement pathway in a little bit of detail. The complement cascade is activated by serum antibodies via the classical pathway, which results in bacterial lysis and opsonization of meningococci.

In the absence of specific meningococcal antibodies, complement mediated function can be activated by the alternative pathway. For both pathways of complement activation, the final common pathway is formation of a lytic membrane attack complex which results in cell lysis.

The role of bactericidal antibody in immunity to meningococcal disease was demonstrated by studies that looked at the incidence of meningococcal disease in age specific prevalence of bactericidal antibodies. Second, by studies in military recruits and third, by the increased susceptibility to meningococcal disease observed in individuals who have late complement component deficiencies.

Studies done in the 1960s by Goldschneider and coworkers have shown that at birth, one half of infants were noted to have bactericidal titers due to maternally acquired antibodies. As the maternal antibodies declined, naturally acquired antibodies increased gradually with age.  The highest incidence of meningococcal disease shown here in a simplified figure occurred in infants between six and 18 months of age when the bactericidal antibody concentrations were lowest.

In another study, baseline sera was collected from military recruits when they entered basic training. There were 60 cases of meningococcal C disease that occurred during the course of training and baseline sera in the disease isolate were available for 54 of the individuals.  Only three of the 54 individuals had bactericidal antibody in the sera that was obtained prior to exposure to the disease isolate.

The bactericidal assay used in the study was designed primarily to determine whether an individual did or did not have bactericidal activity against the meningococcal strain.  The assay used intrinsic complement source and the volume of sera comprised about 25 percent of the reaction mixture, so in essence the sera was diluted one to four.

This study shows that almost all individuals who develop meningococcal disease lacked bactericidal antibodies to their pathogenic strain prior to exposure, and that protection against meningococcal disease at the time of exposure is dependent on circulating antibodies.

In 492 recruits, a baseline sera and nasopharyngeal culture was obtained. 438 individuals had bactericidal antibody in their sera at the time they started basic training. None of these individuals developed disease. Fifty-four of the individuals initially lacked bactericidal antibodies prior to exposure to the men C epidemic strain.

Of the 24 individuals who were exposed to the strain, 13 individuals became colonized with the disease causing strain and lacked bactericidal antibodies to the same strain. This population constituted the people at most risk for developing meningococcal disease, and as such there were five confirmed cases of men C disease in this population for an attack rate of 38 percent.

Lastly, individuals who have deficiencies in late complement components five, six, seven or eight lack the components needed to form the lytic membrane attack complex. These individuals have markedly increased susceptibility on the order of 5,000 to 7,000 times the risk to develop meningococcal disease.

Dr. Zollinger highlighted the important characteristics of a serologic marker of protection. The marker should be a measure of a biologic function important in protection from systemic disease, and with a validated assay function antibodies can be measured following vaccination in a bactericidal assay and these antibodies can reflect vaccine protection. SBA with human complement is consistent with an in vivo biological mechanism of protection.

Use of hSBA has been used as a measure of immunogenecity in recent vaccine approvals, and vaccine seroresponse and postlicensure vaccine effectiveness estimates also trend in the same direction.

The experience with the meningococcal C conjugate vaccine in the U.K. is well documented. These vaccines were introduced in the U.K. because there was an increased incidence in overall meningococcal disease which was caused mainly by a virulent strain of serogroup C, subtype 2A. There was also increased awareness that a C:2A clone was an emerging cause of meningococcal disease in Canada and Spain.

In the year prior to the introduction of meningococcal C conjugate vaccine, the incidence of men C disease in all ages was 1.5 cases per 100,000. There were 2,418 confirmed cases of meningococcal infections, and also the proportion of men C disease increased from 26 percent in 1994 to 34 percent in 1998.

Lastly, the case fatality rate in adolescents was high, particularly because the meningococcal C:2A was the predominant sero subtype in the U.K.

This slide shows that the deaths due to meningococcal disease were highest in children less than a year of age, which is the peak on the left, and then in adolescents, which is the peak on the right.

Meningococcal C conjugate vaccine was introduced in the U.K. in November of 1999, first in infants and adolescents. These age groups were the groups were mortality rates and the risks for outbreaks were the highest. Infants received meningococcal C conjugate vaccine with their routine childhood immunizations.

Then a catch-up vaccine was undertaken for the remaining children less than two years of age. The children five to 11 months old were given two doses of the vaccine and children 12 to 23 months old received a single dose. Children two to four years of age were vaccinated next, followed by vaccination of the remaining pediatric cohort.

Vaccine introduction was temporally associated with a significant reduction in meningococcal group C disease in the vaccinated population. The incidence of serogroup C disease remained low in 2002 to 2004, which supports the vaccine effect.

Continued low incidence of meningococcal disease occurred from 2004 to 2009, supporting that the control of meningococcal disease was attributed to vaccination through direct protection to the immunized population and through indirect benefits to the unimmunized population.

Overall effectiveness four years after vaccination was at least 83 percent in children aged five months to 18 years of age, where vaccinated is part of the catch-up campaign.  Infant immunization was associated with a short duration of antibody titers and was consistent with trends of decreased vaccine effectiveness.

A change in the routine immunization schedule to include an additional dose in the second year of life provided sustained protection and reduced the number of breakthrough cases.  These findings support that vaccine introduction and use was associated with reduced disease incidence, and that declines in circulating bactericidal antibodies was associated with decreased vaccine effectiveness and resurgence of disease.

In conclusion, conferred effectiveness using a serum bactericidal antibody measurement is supported as follows.  Antibody dependent complement mediated bactericidal killing is a principal mechanism of protective immunity against invasive disease in both children and adults. Individuals who have circulating functional antibodies present at the time of exposure are protected from disease. Postmarketing surveillance data support that meningococcal conjugate vaccine induced bactericidal antibodies directed against the polysaccharide capsule can be effective in controlling meningococcal disease in infants and young children.

Serum bactericidal activity with human complement is consistent with an in vivo mechanism of protection. So all factors taken into consideration, the presence of functional antibodies that are bactericidal measured by an hSB assay can be predictive of protection.

DR. FERRIERI: Thank you.

DR. DURBIN: I had two questions. My first question relates to, most of the data presented for the bactericidal assay has to do -- was done in adults and children older than two. I wondered how much data we have in terms of relating the bactericidal assay titers in children less than two with susceptibility to disease.

My second question is, how would maternal antibody confound the ability to measure a response to vaccine if there is maternal bactericidal antibody.

DR. BASH: I am going to answer your second question first. Depending on whether seroresponse or end point titer after a certain number of immunizations after a two, four and six month immunization schedule by seven months of age, the presence of maternal antibody has substantially declined.

But also, in comparing your unimmunized group to your immunized group, you can get a sense of what proportion has antibody decline over time versus background antibody titers. For the most part they are not that high. So I think there are ways in the clinical trial design to either incorporate this into the end point that is being measured or not or understand it by comparison of vaccine versus non-vaccine groups in order to figure out what contribution the maternal antibody may have or not at that pre-immunization two month visit.

So that is something that is looked at in the data, if that answers your question. I am going to have to ask you to repeat the first part of the question.

DR. DURBIN: My first question was, a lot of the data on the bactericidal assay in terms of looking at that as a biological marker of susceptibility to meningococcal disease was presented from data from adults and children older than two. I wondered how much data we have on children less than two, looking at that.

DR. BASH: There is some data in infants, not so much with the conjugate vaccines, except from the monovalent experience that the EU has had, especially in the U.K. Much of that data was generated with rabbit complement. So if you are really asking for very specific human complement mediated protection, there is not as much of that. Although the seroprevalence studies, those original landmark studies, did incorporate that age group. The biggest comparison, or the most relevant inverse association between antibodies and disease was in the youngest age groups.

So I think that information is very supportive that there is not something unusual in the mechanism of protection under two years of age.

The other piece of information that I think contributes to this we will talk about more tomorrow. In the context of group B vaccines, the relationship between bactericidal antibody and protection is similar, whether it be poor protection and poor response or good protection and good response, but that is not -- the measurement doesn't have an age dependence. The response might have an age dependence, but the assay actually seems to mirror the effectiveness quite well regardless of age group.

So the experience in New Zealand for example focused on infants was very consistent between their immunogenecity and their observations post implementation. That was with a human complement assay.

So from the U.K. we have rabbit complement data that is supportive. From New Zealand we have human complement data that is supportive. I think the very original sero epidemiology data is also supportive for that infant and under two year age group.

DR. DURBIN: Thank you. That is very helpful.

DR. GELLIN: I think this is a related question. We have talked a lot about complement in assays, but I am wondering about complement in the age less than two. What do we know about the maturation of the complement system and whether there might not be relative deficiencies of complement that might correspond to this as well. So if you had antibody, that might be fine, but there is a cofactor that we are not talking about.

DR. BASH: I think that is a very good question. I am not a complement expert, so I don't have the detailed answer to your question. But I do think the same examples are relevant in the sense that the generation of antibody against the capsule to the monovalent C vaccines was clearly very effective in the U.K. in preventing disease.

There is no evidence that the mechanism of protection in infants is anything other than what it is elsewhere. It is not more opsonic versus complement mediated. The mechanism of protection is the same.

So although we are measuring in an assay generally using adult complement because that is an easier source, that assay is predictive of how the antibodies are working in an infant, and the infant obviously has their own complement.

I do think other people have had infant sources of complement, whether from agammaglobulinemic people, and those work. So I'm not aware of any -- I think it is an important question; I'm not aware of any evidence that would say that it is a concern in this situation.

DR. FERRIERI: That is correct. Serum complement develops very rapidly to normal and functional levels in the postnatal period. So in the very premature infant, there is a compromise of one's complement mediated bactericidal activity. But it becomes very normal. This is true for polymorphonuclear neutrophil function as well. Unless you have an innate defect in complement factors, one's intrinsic complement activity is very good. So the deficiency for some pathogens in the newborn, it is a deficiency of immunoglobulin of specific antibodies that is critical rather than a deficiency in intrinsic complement.

I'm not an authority on complement, but I have to talk about it related to various bugs. Does anyone else want to add to that discussion? Anyone who is a bona fide card carrying complement authority on the panel who would like to add to that?

Any other comments or questions?

DR. SCHOOLNIK: One of the striking sidebars to Dr. Lee's presentation was the increased incidence of meningococcal disease in adolescents, when contrasted against the increasing development of bactericidal antibodies that Goldschneider showed as people aged through middle childhood and into adolescence.

So there is a disconnect between the prevalence of bactericidal antibodies in adolescents, which is relatively high, and the incidence of disease in that population. That is not only found for invasive meningococcal disease. There are some other infectious diseases in which adolescents are also more susceptible compared to middle childhood on the one hand and people under 20 on the other. So it is a unique period of susceptibility for some infectious diseases. The other one that comes to mind is mycobacterium tuberculosis.

I am just wondering if anyone has an explanation for why there should be this increased disease incidence in adolescents, whether it has a biological basis or a sociologic basis. I wonder if anyone has any thoughts on that. But obviously it is a period of increased risk. That is a group that we should be also concerned about in addition to kids less than two.

DR. FERRIERI: When we had an outbreak several years ago in a community outside of Minneapolis-St. Paul in high school kids, their social activities were studied quite a bit, and clusters of disease were seen in kids who gather after school and drink from the same big container of soda pop and use the same straw and so on.

So that is one element. I don't wish to enter this piece of information as a joke. I don't know if there is more of an underlying biological basis for the clusters you see, teenagers, college kids, when you see outbreaks in them. Maybe there is something else that is related to hormones and susceptibility.

Other comments? Do you have a thought, Dr. Apicella?

DR. APICELLA: The military studied this for 40 years to try and figure out why recruits were more susceptible to disease. I really don't think they ever came up with a reasonable conclusion.

The British did a lot of studies on social habits and came up with visiting pubs, smoking, kissing, a whole long list of different things that teenagers do, which may or may not be associated with, but it is real. It has been looked at, but I don't think there is a good answer.

DR. FERRIERI: We are now at a time when we will take a break. We will reconvene very promptly at 2:30.

Thank you, everyone.

(Brief recess.)

**Agenda Item: Open Public Hearing**

DR. FERRIERI: Hello, everyone. We are ready to start the afternoon session.

DR. JEHN: We have received one request to possibly speak at the open public hearing. Does that person still wish to speak? Does anyone else wish to speak during the open public hearing? It looks like silence is affirmative.

**Agenda Item: Committee Discussion**

DR. FERRIERI: Since we don't have anyone from the audience during the open public hearing, we will continue then. We will put Dr. Lee's discussion points up on the screen. Did you want to say anything else at this point, Dr. Lee? Thank you.

We are not going to be voting on any items today, neither today nor tomorrow. So we need to have a rigorous discussion here today on these points. Number one. Please comment on the use of the human serum bactericidal activity as an immune measure to infer effectiveness of meningococcal conjugate vaccines for children less than two years old. So we will start with that.

I will make a brief remark. I love functional antibodies as a measure of looking at vaccine effectiveness. This is a general comment, not necessarily related to meninge. For years in the past when we had other vaccines, non-meningococcal vaccines under discussion here. There was always so much emphasis on ELISA or other immune measurement of antibody concentration. We had to fight for functional antibody assays on a number of occasions. So the joy of being here today is that we are not fighting about or demanding to have functional activity as a measure of vaccine immunogenecity.

The other great piece of information, for those of you who have the burden of measuring this, is that we are talking about polymorphonuclear neutrophil free absent assays. So we are not talking about opsonic phagocytic assays, which makes this in some ways simpler.

So with that as an intro, I will entertain anyone to kick off the discussion now.

DR. GRAY: It seems clear that it is necessary that we have standardized reagents and standardized protocols, should this be fully adopted. I am wondering about the commitment by FDA to make those available. Certainly that is being done by some branches of the government with respect to influenza because of similar great disparities with respect to the serologic assays.

DR. FERRIERI: FDA, who would like to respond to that? Dr. Bash or Dr. Baylor?

DR. BASH: I will start with just the assays themselves. We don't have a mechanism for establishing a certain protocol, but we do have a tremendous requirement for the validation of the assays that are used for evaluation of vaccines.

So the assay validation, the plan for validation, the results of the validation protocols, are all reviewed in detail. So although I agree with you that there would be an advantage in many directions to have set standards that everyone did the same, we haven't had a central laboratory that has coordinated that for *Neisseria meningitidis* the way we have for some other organisms. It hasn't been a focus of effort either through NIH or through us.

There has been an acceptance of certain strains internationally through the WHO. There is a lot of collaborative work that has gone into the development of these assays. From our perspective, the specific assays used for vaccine evaluation, those assays are reviewed in great detail, and in fact can be and have been subject to inspection to observe the assays or to look at the data management of the assays and those sorts of things.

So I don't want to say that they are uncontrolled, because they are not. There is a lot of concern about the assays being reproducible, and for the results that we make judgments based upon to be reliable. But to say that each assay done by different people are the same, that is not the case at this point.

DR. FERRIERI: Did everyone get to hear that in the back? Are you saying then -- if I understand you correctly, Dr. Bash, in the recent past, that FDA has gone to industry relevant to their vaccines for meninge and observed the performance of the bactericidal activity assay?

DR. BASH: Yes.

DR. FERRIERI: Good. There are a lot of other questions here.

DR. DURBIN: I just have a really quick question. In terms of doing the assay itself, how much blood is required? And do you think that would be difficult in very, very young infants?

DR. BASH: Each assay may be somewhat different, but an individual sera would potentially be assayed somewhere between ten and 25 or 50 microliters, depending on the end volume, and generally adequate amounts for repeating or for determining higher titer. For example, in the quadrivalent conjugates, each different serogroup is a different assay.

So it is very doable with infant sera in this context. And in terms of the serogroup B situation that we will talk about tomorrow that Dr. Zollinger mentioned, that really does become a factor in terms of what can and can't be done with infant sera.

DR. FERRIERI: Could you repeat that last sentence about what could not be done based on Dr. Zollinger's presentation? I didn't catch that.

DR. BASH: I am just saying that the volume of sera that is obtained from infants in infant studies is generally not a limitation in the evaluation of quadrivalent vaccines, but depending on how many strains you wanted to try and assay with B strains, then that volume does become an issue.

The other complicating factor is that there is often questions of concomitant vaccines that also need to be assayed with infant sera. So the volume is something that needs to be concerned about, but for the quadrivalents there is adequate sera to do each of the four serogroups when necessary.

DR. FERRIERI: It is a serious thing. I had a maternal infant experimental trial of a vaccine where the draws on the babies, even though they were somewhat older infants at six and seven months, and then later after a booster at 12 months, depending on the skill of those drawing the blood, it is quite a problem particularly for the mothers, seeing children stuck again and again to get a little bit of blood even. So this is a serious limitation at times.

DR. TACKET: We have seen very solid evidence that the assay is difficult to do and requires standard conditions, standard methodologies, set out. But it would be very useful for vaccine developers to have a set of reference pedigreed sera so that even if they are following the methodology to the letter of the law, they can confirm that the sera are at the titer that they have been expected to be. That would also allow vaccines to be compared potentially in the future. So that would be a very important resource if that could be provided.

DR. BASH: I agree. There is meningococcal standard sera that is used for the ELISAs. It was generated at the CDC in the era of the polysaccharide vaccines. I think that your comment is very much appreciated by people in the field. Standard sera that represents the type of immune responses that we see with conjugate vaccines would certainly be an added benefit to the field.

DR. FERRIERI: Other comments from our panel?

DR. APICELLA: Margaret, I would think that given the data that Dr. Zollinger presented with the variability dependent on whether you take a swipe or a single colony, whether you shake the plate, what kind of media you grow it on, that there should be a standardization. How do you compare two products that are tested in two different ways?

DR. BASH: We don't compare two different products that are tested in two different laboratories. Important to this context in the infant studies of new conjugate vaccines is the internal comparison to either pre inflammation or the unimmunized group, so that you have a comparison within that assay.

But also in respect to your earlier comments, the types of things that you are talking about are part of the methods that are reviewed when we look at the validation of the assay. Those things are spelled out, how the bacteria are processed and stored and that is incorporated into the validation of the assay and the performance of the assay as well.

But it is a very important thing to note, that the immune responses in two different laboratories are not necessarily comparable, and we do not compare them in our evaluation of the vaccines.

DR. FERRIERI: Have you assessed the strain used by various companies imposed or suggested, specific strains? What you are asking us to comment upon obviously from all the questions from panel members is not whether this is useful necessarily, but great concern about the uniformity and performance of the assay for us to believe the results of the assay.

Among them are uniformity of choice of one strain, two strains or three. One strain theoretically for the vaccine under discussion, not today, but a vaccine under discussion, you have approved their strain for their assay, correct?

DR. BASH: Yes. For the ACYW135, these assays are really old assays that have been around for a very long time. There are standard strains that are used routinely, and some people may vary with a different choice of strain. But if that is the case, then comparability, encapsulation, the kind of information that Dr. Zollinger discussed, is part of what goes into the assessment of the acceptability of that assay.

DR. FERRIERI: Right. It is much easier for me to accept an assay and its performance when it is again a single constituent such as the capsule. I think that is much easier in deciding upon the strain theoretically and practically.

But then there are levels of complexity in my opinion that are introduced based on multiple antigens that may be present in the experimental vaccine. This is where I have more difficulty and need reassurance on those strains chosen that represent the putative antigens, that most of them are present on multiple strains of that serogroup, for example. Depending on the antigen, the expression varies as you well know.

So that is a whole other issue of complexity when talking about very complex multi-antigen vaccines.

DR. APICELLA: I want to go back to that, Margaret. When you have a vaccine and you are looking at it for approval, doesn't it have to be as good as existing products on the market?

DR. BASH: Yes.

DR. APICELLA: How can you evaluate whether it is as good if they are using two different methods to present to you? If I use rabbit serum as complement source and someone else uses human serum as a complement source, and I know that rabbit serum enhances a lot of things that are irrelevant to the process.

DR. BASH: In the licensure that we have had already of the conjugate vaccines in two-year-olds and above, the non-inferiority to a licensed vaccine has involved a randomized trial in which people within a single trial received either the currently licensed vaccine or the investigational vaccine. So sera from each of those groups were then assayed in the same assay and the details of how these sera are even arranged on the plate, does it represent the same randomization as what occurred in the clinical trial, that level of detail is reviewed to try to insure, to whatever degree possible, that there is not a bias introduced by the assay. So it is an internal comparison within that assay run in the same place, and presumably reflects the same randomization that was instituted within the clinical trial.

DR. FERRIERI: But is it not true that what you have just spoken of was measuring anti-capsular antibodies, for example induced by a conjugate vaccine versus a non-conjugate polyvalent capsule antigen vaccine?

DR. BASH: Yes. So my comments today are focused on the conjugate situation. We will have even more complicated discussions tomorrow, I'm sure.

DR. FERRIERI: Maybe we can't stray that far today, but obviously the interest exhibited and shown by members of the panel has to do with uniformity, of performance of assays, how do you control for strain variation and all the other complex constituents of this. Even though on the surface it is a relatively simple assay, there are many variables that can be distorted, subjected to little tweaking and substitutions, et cetera.

DR. SCHOOLNIK: I am just going to try to seek a little more clarification along the lines of the nature of the oversight that the FDA has of the serologic responses to a manufacturer's vaccine.

What I have learned so far is that you review the protocol, but what I don't yet know is whether the performance of the assay in the manufacturer's facility is actually observed. That is the first question. Whether the FDA attempts to confirm the results by testing in its own laboratories here, to see if the results are comparable for a random subset of sera. Whether there is a standard panel of well-characterized sera as Dr. Tacket suggested that is given in some sort of blinded way to that laboratory to see if they get the same results.

I just don't know at this point how far the oversight actually goes. I guess that is my question.

DR. BASH: I will start on this, and then there may be other people who want to provide additional information.

Fairly early in development, especially when there is a vaccine like meningococcal vaccine where we anticipate that the real effectiveness end point may be serologic, there is a lot of interest and effort spent with the manufacturer in the development of the assay. So when we know that it may not be a clinical end point study, then these assays are focused on so that ideally they are fully validated and incorporated into the end points of your pivotal studies.

So the early development of the assays is reviewed under IND along with clinical data, clinical trial plans and information. In terms of having a validated assay for pivotal data, generally the validation plan is submitted, or it may just be the assay validation data itself. But the method of validation and the data generated in the validation study is all reviewed.

In that are incorporated the controls, how the complement is screened and selected, and what components are in place to monitor the performance of the assay over time. So for instance if you could trend and say is the assay performing the same over the entire duration of this clinical development, and within the context of individual studies the effort is to have say a certain complement source for the entire study, so that you would eliminate those shifts that might happen if you were to change a reagent in the middle of assays.

So each of those aspects are part of what we look at in terms of assay validation.

In addition, when data are submitted and the immunogenecity data to support a license application are submitted, those are reviewed in data sets. The data sets are looked at, so that the real output of each of these assays, the controls, the performance of trends within the different assays runs, can all be evaluated.

Again, this is in paper, so up to this point there is nothing that is done in the laboratory. If there are questions or concerns or if the immunogenecity is felt to be of significant enough importance, this kind of information can be reviewed just like any other by a research monitoring that can be done. So inspectors can go review everything from how the assay is performed to where the record is of what has been done, and compare that with what has been submitted.

So we have the ability to look at the assay in detail. I think that your question is very important, because we are talking about efficacy. This is the effectiveness end point. And historically many assays were used to monitor changes in a vaccine production or whatever. But here, it is essentially taking the place of the clinical end point.

So we have the ability to treat that data as we would clinical end point data, go out and inspect, go out and look at what is the training of the people doing this. We have the ability to do all of that.

We have not done that second question that you asked, where we get a subset of clinical specimens and run them in our own assay. In fact, I do do these assays, but I would have to say, my lab is not to the standards that would be expected for clinical trials. I have an experimental lab, a research laboratory. So in fact, I might introduce more problems than good in doing that.

The honest answer is, we do not have a serology section dedicated to doing that kind of work. I know that in some countries, the immunologic evaluation of vaccines is done by a separate dedicated group that is government funded, and that isn't the situation that we have here.

The CDC has done a lot of development of these assays in the past, and has contributed, but they also do not receive sera from clinical trials to compare results. So that aspect of your question we do not do.

DR. APICELLA: The third part, which would not require that you maintain an expert lab, but that you have a panel of blinded sera that you send the manufacturers, which is one way that a national reference laboratory gets validated by supernational reference lab, blinded panels of samples.

DR. BASH: I think that it is fair to say that that is a gap. The sera that were developed by the CDC functioned very well in standardizing ELISA assays, and also functioned very well in rabbit complement assays. But the titers are very, very low in human complement.

Our preference for the relevance, the added relevance of using human complement has shifted us to using that assay in spite of the fact that the established standard sera have such low titers in a human complement assay that they can be used, but they really don't serve the purpose that you are asking for.

So they are not available now, is the real answer.

DR. APICELLA: Thank you.

DR. FERRIERI: As an extension of that though, if you were planning this de novo, in an ideal situation you would have those standardized antisera to any relevant antigens that are part of a new vaccine. This would be the ideal situation, so you feel that you can stand behind any assertions made as to the immunogenecity.

Since everything is hinging on the bactericidal activity in the case of the meninge B vaccine, we are not doing efficacy trials. This is not like *Haemophilus influenzae* or something. So much hinges on our credibility of the assay results that I would think that at a minimum you would be controlling for having a standardized serum against each relevant antigen in a vaccine. Number two, that there would be a standard strain that would be chosen that you could stand behind the choice of industry, the choice that industry has made that you can verify that that was the best choice, for example, of one or two strains or whatever.

I know this sounds extraordinarily stringent, but I think that our standard has to be very high, in keeping with the high standards that FDA has imposed in the past on many other new vaccines.

So maybe other members of the panel disagree. I think Dr. Schoolnik and I may see eye to eye on this. He is nodding his head yes. This is a very tough thing. I have sat in this position before in past years with other new vaccines being presented, and I identify with the groans that come from those in industry who are presenting new information. But I just think that that is the standard we have to have, and we have to continue to fulfill the mission of FDA and the faith that the public has that we are doing our very best. I know this sounds like some platitude, but I really mean it. I see Dr. Apicella nodding his head yes, too.

DR. GRAY: It seems from my reading that there are many different strains that could be appropriately chosen for vaccine constructs, and a number of approaches are being taken. So I'm not sure I agree that we should select the strains beforehand for the vaccine constructs to be tested.

But I do think you could follow the paradigm that the CDC has used, and providing a limited amount of reagents to pharmaceutical companies that are suggested to follow a standardized protocol, such that you could make some sense of their serologic approach and assist them in adapting approaches that would satisfy FDA constraints.

I think the CDC did this basically by contracting with GMP organizations, so the burden was not placed on the CDC research laboratories, which they would argue that they were probably not well suited for that. So it was a limited contract, and the parties would petition -- generally it was set up for the public health laboratories, but parties could petition the FDA for those specific reagents.

DR. FERRIERI: So I am not misunderstood, Dr. Gray, I am not saying FDA has to choose the strain. There has to be consensus with what has been chosen to work with. I hear them saying that is the strain that we endorse.

Other comments on this first discussion point?

DR. TACKET: I think we can probably figure out a way to standardize the assay based on the parameters that we have all been talking about. Are there data showing that the bactericidal assay is equal with protection in children under two? We have seen that for the older children, but is there sero epidemiology data that correspond with protection based on the assay?

DR. FERRIERI: Thank you, Dr. Tacket, for getting us right on beam again on your question. I appreciate that. It gives them a few seconds to assemble their answer also.

DR. LEE: You are right, that is the very question we are asking. From the Goldschneider studies, individual protection was shown, but the assay was slightly different than the assays that are used today.

So there is a leap of faith that the use of human complement was the source of complement used to show individual protection. But the other piece is that today's assay is reliable enough and accurate enough to detect the functional antibodies that are bactericidal. So that is the dilemma for young children.

DR. TACKET: There are no data for children under two?

DR. LEE: For human complement, there is none.

DR. FERRIERI: So this is quite a leap of faith that we have to make to endorse or agree that this is useful for children under two. We have no negative data, is that true, to suggest that it is not useful? We don't have negative data, but we don't have data that really answers her question.

DR. LEE: The sero epidemiology data from Goldschneider did encompass from birth through teenage years. In that there were two collections of sera from two different time points. One was from the Texas Medical Center. I can't remember right now where the other collection of sera were from.

Those were not active sera. Those were from serologic banks. So in that sense, the sero epidemiology, the classic graphs that show antibody goes down, disease goes up, antibody goes up, disease goes down, those were using extrinsic human complement added to stored sera.

So I do think that that fundamental historic data does relate to the age group that we are talking about, and is supportive of the concept that the primary basis of protection in this age group is in fact complement mediated bactericidal antibody.

DR. FERRIERI: Even though those sera that were studied in that age group were not post vaccination, but were assessing the natural development of bactericidal activity, it may be legitimate to translate that data to the post vaccinee serum and its activity. That is probably the fairest statement one could make.

Does that sound acceptable to you, that it is an inference from sera studied in that age group that the development of natural bactericidal antibody? I must say that although we think that that evolution of natural bactericidal antibody against *Neisseria meningitidis* or *Haemophilus influenzae* in the pre vaccine era was specific for the organism by exposure that did not lead necessarily to disease.

We don't really know in my opinion what that bactericidal activity reflects. Does it reflect specific antibody or is it the evolution of sophisticated immune responses, acquired immunity that may not be specific antibody? I don't know that we have data, because those sera were never assayed for specific polysaccharide antibody or any specific antibodies. Is that true or not? Complement is curves.

DR. BASH: I would need to get back to you about the additional aspect of whether or not the antibody was characterized as anticapsular antibody or not, in terms of that pattern of protection from disease in the original Goldschneider data.

But I do think that there is experience with meningococcal conjugate vaccines in the infant age group, if not in the U.S., elsewhere. It is very supportive that the development of functional antibody provides protection. In fact, the absence of functional antibody identifies a group that is at risk for disease. If you think back to ten years ago, we very much were concerned with priming as one of the benchmarks for thinking about the effectiveness of these vaccines. The experience in the U.K. has very much changed that for both Hib and meningococcal disease.

I think it is important from a product standpoint that we see the development of priming, because we expect a conjugate to prime. But we now understand that that is not adequate for disease protection. It is from that observation in the U.K. between the falling of functional antibody and the recurrence of disease.

So I think that that is very supportive of what we -- in every situation in which it has been observed or studied in respect to conjugate vaccines, the information agrees with what we understand the pathogenesis of the organism is and natural immunity. So we are not seeing a discrepancy between vaccine induced protection and what we understand to be natural protection.

DR. FERRIERI: I agree with you. I think invoking the United Kingdom data on the meninge serogroup C vaccine is the strongest support for the linking of the hSBA with -- they used human serum in those assays, I can't remember, or rabbit complement source?

DR. BASH: The standard U.K. assay was with rabbit complement.

DR. FERRIERI: Rabbit, yes. But the outcome and the protection and lack of protection that waned as correlated with -- I am using that word the verb, not a noun -- as correlated with clinical outcome I think is very strong.

Other comments before we leave this subject?

DR. MC INNES: Picking back up on that, as I recall in the development stages of those meninge C conjugate vaccines, there was demonstration of bactericidal antibody in a whole spectrum of age groups, including younger children. So I am comforted very much by that.

In addition, the demonstration of efficacy, effectiveness and waning thereof as time went on and subsequently reintroduction and again waning of disease, I think is extremely supportive and consistent with the performance that we have seen of immunity induced by polysaccharide conjugate vaccines. I think this is a pattern that we see time and time again.

So personally, I think the approach to using bactericidal antibody in serum transfer effectiveness. I don't see a basis to not accept that in children younger than two. I think all the issues on the table are very valid, but I think it is a reasonable approach.

DR. FERRIERI: I think Dr. McInnes has really summed it up. This will bring to a close item one. I see a lot of heads nodding, that that is the strongest data in support of using that as a biological immunological marker for effectiveness. All of the points we have raised about the ideal world of what we would like to have standardized, whether they are sera or confirmation that the strain used to measure the bactericidal activity conforms to what you think would be good, and that you verified that it is good.

At the end of the day we don't have any information to support that there is anything better than this, and that this is what we are left with.

Yes, Dr. Gilbert. This will be our last point before -- the next items is a very important and critical one, and I don't want to shortchange it.

DR. GILBERT: I agree that this is a reasonable approach. But my comment has to do with how one might evaluate a surrogate for protection from a statistical point of view.

Whereas we apparently don't have data to do that for kids under two, I think there is an opportunity to employ some of the literature on statistical methods for evaluating a surrogate to understand more fully the reliability for the bactericidal antibodies as surrogates for the older age groups. To the extent that that is reliable, that provides at least some greater basis to inferring predictive surrogacy for the young kids.

Going through the materials, a main way to build evidence for a good predictive surrogate is to study correlations of antibody levels with case rates, both natural induced antibodies and vaccine induced antibodies. That is a very good thing to do, and looking for strong correlations is maybe the primary way for people to look for good evidence there.

Where I would provide advice to the FDA about encouraging groups doing studies to go to the literature on surrogate end point evaluations, to apply those methods where possible. I will mention three examples of that quickly.

These are things that could have been done but haven't been done, from what I can tell. For about 20 years now, there has been in the statistical literature an approach to evaluating a surrogate end point called the Prentiss criterion, where you look at the rate of disease as a function of the antibody titer, not just threshold but the whole range of antibodies. Then you do that separately from the vaccine and placebo groups or for the vaccine and control groups.

If those curves superimpose, then you have evidence that that titer is a reliable surrogate end point for the true clinical end point. In fact, looking at the data that were available here, the whole study in 2003, the curves are seen as superimposed, so that gives me some assurance that it might be a valid surrogate.

Then also, for about 20 years there has been a statistical literature on surrogate end point evaluation using meta-analysis. What you need is, you need groups which could be subgroups within an efficacy trial or distinct efficacy trials, or just many subgroups combined across a handful of efficacy trials. For each subgroup you need a group level vaccine effect on the titer, and you need a group level effect on the clinical end point. Then do a scatter plot of those group level effects and then formally employ these higher meta-analysis methods to see just how strong that correlation is, and also to predict what the vaccine efficacy would be in the new setting, based on just measurement of the titer in that new setting.

The documents we have, a kind of informal meta-analysis was done, but there is room for improvement using those statistical methods that have been published.

Lastly, in about the last five years there have been new statistical methods that have been developed to try to estimate the vaccine efficacy as a function of the individual titer. Seeing plots like that would provide additional information.

DR. FERRIERI: Thank you, Dr. Gilbert. Dr. Lee made a point with her first presentation that we would not be discussing surrogates today. We are talking about immunological markers of protection or effectiveness. So

I will take the prerogative as Chair for us not to pursue this any further, if that suits FDA. Dr. Lee is nodding her head.

So we will move on to item two to address. I will read it again. It is on the screen. Please discuss postlicensure studies that might be needed to further evaluate the effectiveness of meningococcal conjugate vaccines in children less than two years old.

This is very critical information for FDA and for industry, what do we expect, what would we want, how impossible are the bars to reach. Who wants to kick that off? Please, Dr. Debold.

DR. DEBOLD: First of all, I would like to ask a question. I got a little confused going through some of the presentations. About how many children per year under the age of two are we talking about get this disease? There were rates per 100,000.

DR. FERRIERI: If you are talking about the U.S.?

DR. DEBOLD: Yes, for the U.S.

DR. FERRIERI: U.S. it is fairly low. Dr. Cohn presented that epidemiological data.

DR. COHN: If you look at the last couple of years of epidemiologic data, there has been about, I calculated six months to 59 months that were about 80 cases of C and Y disease a year in that group. I think six to 24 months is more like 50 or 60.

DR. FERRIERI: What did you just say?

DR. COHN: Those were serogroups C and Y cases.

DR. FERRIERI: Yes, but B is the predominant serogroup for under one year of age.

DR. COHN: So there are about 150 cases of serogroup B in that same age group.

DR. DEBOLD: So that is a pretty small number.

DR. COHN: To put that into perspective, each birth cohort is about four million infants.

DR. DEBOLD: I understand the concern about the difficulty in directly measuring efficacy and effectiveness when the incidence is so low, but because the incidence is as low as it is, I think from the perspective of the public, they are going to have a fairly high bar in terms of wanting to know that the vaccine truly is effective and that it is safe.

The tolerance for problems related to safety and lack of effectiveness I think will be fairly low, considering that from the reading that I picked up, that most people will encounter this disease over the course of their life and have an asymptomatic exposure to it, and end up having protective antibodies. So when we start vaccinating everybody, infants as well as young children and adolescents, I think we need to know that the net effect of that experience is going to be better than what we currently have.

Which brings me to another comment that I wanted to make on this topic about what happens during the first six months of life. Since we are talking about infants and we are talking about measuring postlicensure effectiveness, I think we need to be very careful to measure changes in disease in children that we would have ordinarily have expected to have had protective antibodies from their mothers.

Do we know what happens to the nature and the quality of maternal antibodies if they are conferred by a mother who had direct exposure to the natural disease versus being vaccinated? Do we know whether we should expect disease to be happening earlier and earlier in life than what we currently observe?

Those are two concerns I have. I have a couple of other comments, but I'll stop.

DR. FERRIERI: Thank you, Vicky. Safety is always our primary concern. We also discuss effectiveness. The general public expects us to present only safe vaccines, but Vicky has posed another important question regarding the antibody and maternally transferred antibody.

I think, Vicky, everywhere you mentioned the natural disease and acquisition of antibody, you probably meant exposure to the organism and colonization, then invoking antibody response, if I understood you correctly.

DR. DEBOLD: That is what I meant, thank you.

DR. FERRIERI: Would someone from FDA like to address Dr. Debold's points, please?

DR. BASH: Your comment about the relative risk that an individual infant might face for this disease is very well taken. I think that it is imperative upon us to very well describe the potential benefit so that that can be weighed by people who make decisions about how these vaccines would be best used in the population can make the best possible decisions.

Certainly as Dr. Ferrieri said, the safety needs to be well described, and also the effectiveness that is expected and the limitations of that effectiveness needs to be well described, so that decisions can be made about when and where to best use these vaccines. So we are very sensitive to that point, is the best that I can say about that.

DR. APICELLA: From personal experience, when I was in the U.S. Air Force in the 1960s, we had an outbreak in three months of 37 cases on one base. You want to have something like this readily available to be able to apply it to a population if you have to.

So I think there are two issues here. One is, we need these vaccines because that can happen again. Two, people have the right to have the option to use it if they want to in their children.

DR. FERRIERI: I think those are very important. It is critical that we have an effective serogroup B vaccine, which has eluded us for decades and decades, as Dr. Frasch and others in the audience know.

I think Dr. Debold is correctly challenging us to the wall. In infants under two years of age, is all the hoopla worth it given in the U.S. at least, the low frequency of disease. That is a tough one, Vicky, as you know. Those of us who are very pro vaccine think, yes, we need to have it because there are deaths due to B and we don't just want to think about the U.S. as the center of the world. Worldwide B is very important.

So we have to think very globally about what the vaccine needs are. I think this is a very worthwhile endeavor for us to pursue, and it is going to be valuable in all age groups, I hope.

DR. DEBOLD: I wasn't trying to suggest that development of the vaccine is something that is useful or shouldn't be pursued. I am just trying to say that I think given there has been so much discussion about inferences and estimates and correlates and all the is sort of thing, we need very large well controlled postlicensure studies that clearly demonstrate true effectiveness. We have got to have it in order for the public to feel confident that indeed the vaccine truly is effective.

DR. FERRIERI: I really appreciate your getting us back on target right now also, Vicky, regarding postlicensure. Why don't I just kick it off by saying a couple of things on my wish list would be that we would be monitor postlicensure the dynamics of decline of antibody as one fancy way of looking at it; does antibody persist, and how are we going to study that in the vaccinees.

Then the other thing that I am keen on is looking at new isolates of meningococcus serogroup B that we find in individuals who have disease, and are they strains that the post vaccination sera would be able to kill. Has there been enough mutation, are there point mutations that have occurred in the critical antigens, for example.

Then maybe a third wish list -- I have lost my train of thought, so we will let Dr. Gray pursue that.

DR. GRAY: The obvious thing is, with 90 percent of these illnesses being captured by hospitalization, is to do the direct estimate through the case studies of who has been vaccinated and who has not.

But in addition to what we have just heard, Dr. Ferrieri's comments, what about the relative carriage of B? How do you expect that to be changed, should you introduce a vaccine? Could that be an indicator of some value?

DR. FERRIERI: Thank you, Dr. Gray. Would FDA like to respond to that?

I did think of my third point. I don't have a cognitive problem, but as the day goes on you forget a few things. Also, the role of any work we could do in animals perhaps in assessing the activity of post vaccine sera, for example.

DR. APICELLA: In response to Dr. Gray's question, the military has been vaccinating for years, since the early 1980s. They did not see an increase in colonization due to B. So at least in adults or young adults, that hasn't been a problem. They didn't see disease due to B, which I have never understood why.

DR. FERRIERI: Something we didn't touch on here, and we can't pursue from a biological and scientific point of view I have always believed that many are called and few are chosen when it comes to meningococcal disease. There are innate immune genetic susceptibility issues that can also perhaps explain why some individuals do and do not develop disease. That is an area that I don't feel I fully understand yet.

DR. DEBOLD: This is a question on effectiveness. You all mentioned a couple of groups that didn't develop antibodies, people who had complement deficiencies and other people who were exposed that didn't. Do we have any evidence that they will develop antibodies if vaccinated?

DR. FERRIERI: I could just mention that those individuals with what are known as the late complement component deficiencies that are inherited, complement factor C5 through C8, they are not non-responders as far as I know to meningococcal vaccines. They are susceptible to infection, and can get repeated infections.

When we have a child who presents with meningococcal disease, invariably we look at their late complement components, and if abnormal we would test other family members. Those are individuals including the index case that need to be vaccinated. Unfortunately we don't have a serogroup B vaccine.

That answers part of your question, but there was another element of your question about other non-responders. I didn't pick that out of your presentation today about non-responders. Dr. Lee, did you want to answer that?

DR. LEE: Just to make the point, Vicky, that complement mediated bactericidal killing is the predominant mechanism, but there are also other mechanisms of protection. So for the late complement component individuals, opsonization might be the more important factor. So these individuals don't die, which means that they have another mechanism at play.

DR. FERRIERI: There are always going to be a small number of people who don't respond to any vaccine. This was truer with the purified polysaccharide vaccines. When conjugated to other proteins, this becomes a much better vaccine and very protective in children, as exhibited by the historical database we have on HIV conjugates and non-conjugate, and what the outcome was in children.

But in terms of meningococcal vaccines, we definitely like the polysaccharide conjugates, but there are deficiencies. They don't cover everything, and we don't have the B vaccine. But I would have to say that non-responders do not comprise a problem as of this moment with past current vaccines for meningococcus.

DR. GELLIN: Just a couple of comments. I want to back up to the previous discussion that Vicky started with.

I think that we have to remember that we are here advising the FDA on products coming forward. That is a separate discussion from the ACIP, who makes recommendations on how to use products. So without a tool, then you can't even apply it. So just to keep those lanes clarified. This is trying to make sure that as the products come forward they meet the FDA's requirements, then can be further recommended.

As far as the question two, I think we also have to acknowledge that there are huge systems in place, and maybe Amanda wants to comment on it, but the surveillance systems that are in place to look at this stuff. It is not like these things are just out there and you push a button and you get a number. What she presented represents a huge amount of work over a long period of time to look at trends.

So I think maybe a part of this is just to reinforce how important those existing systems are, so you can measure the impact of things that are going to be incorporated.

With that is the degree to which there might be an opportunity to look at vaccine failures, so that when these few cases might come up down the line, as Dr. Ferrieri mentioned, nothing is 100 percent, but there will be an opportunity, and to try to think ahead of time what are the clinical, epidemiological, laboratory -- what are the things we want to be looking at to be able to evaluate those few cases to be able to further refine what it is that happened.

DR. FERRIERI: Thank you, Dr. Gellin. To summarize so far, among the things we would recommend would be to look at the new strains that cause disease. One would study them genetically and antigenically to see whether they have changed from what we anticipated the target strain and subject of the vaccine should have protected against.

So all new disease strains would be examined carefully, the consideration of looking at protective bactericidal antibody against those strains and whether it is not there, whether it has waned, and in general looking at the post vaccination decline of the antibody against the vaccine constituents when possible.

Dr. Schoolnik, you were nodding your head. Did you wish to add something?

DR. SCHOOLNIK: I am just agreeing with your list. I think it is an excellent summary.

DR. FERRIERI: Thank you. We are really open to other thinking out of the box items. Let's hear more.

DR. GILBERT: I have a question for clarification. I am new to meningococcus. How many vaccine failure cases under two years old is it realistic to study over the next few years, versus studying failures naturally who didn't get the vaccine? I imagine that latter group, it would be possible to look at hundreds of cases and try to see if it is very rare for cases to have an absent anti-bactericidal titer.

DR. FERRIERI: Wonderful question. Dr. Bash or someone from FDA, would you like to comment on it?

DR. COHN: I can provide some comment. Since conjugate vaccine recommendations in adolescents, so for the whole adolescent cohort of 11 to 18-year-olds over five years, we have reports of about between 30 and 40 vaccination failures, so just five or six a year. We have actually made some inroads and efforts to try to collect sera on all of those cases, but it is actually very complicated, because typically we don't hear about the cases for awhile after they have occurred. It would be very few.

DR. FERRIERI: So they would have developed antibody against the new infection by the time you try to bleed them.

DR. COHN: Right. So I would expect in infants that it would be a couple a year, not several.

DR. FERRIERI: That poses some difficulty, but not insuperable. But I think we can expect there to be mutations that will occur over time. I don't know what the rate of them would be, and I wouldn't dream of predicting this from a statistical point of view, Dr. Gilbert.

But I think this is the nature of the beast. The organisms are exciting and they continue to evolve.

DR. DURBIN: I have a question. It was very explicitly stated at the beginning that we are not talking about surrogates of protection or correlates of protection, but I would ask, in postlicensure studies in age groups greater than two, why can't studies be done to try to determine a correlate or a surrogate of protection?

DR. FERRIERI: FDA, do you have a comeback on that?

DR. BASH: I think the comment was meant to not get into a debate about what is a surrogate and what is a correlate. I think that the evidence would support that bactericidal antibody is a surrogate of protection, and that the hSBA assay correlates with protection.

But that is my understanding of those terms. When we have meetings where -- I was at a meeting six months ago where the person defined those in exactly the reverse from the way I understood them. So I think we are talking about surrogates and we are talking about correlates, but we don't want to get caught up in the terminology.

DR. DURBIN: Just as an aside, I was at a WHO meeting where the European understanding of correlate and surrogate were the exact opposite of our understanding.

But what I would wonder going forward with this, whether or not studies will continue following antibody titers over time postlicensure, and strengthen that in so that we have those data in infants under two.

DR. FERRIERI: Recognizing the difficulty of obtaining blood from young infants, which is a challenge, we need to have a newer technique, other than doing venipunctures in the antecubital space. In very young infants, many of you know that you can do heel sticks and collect limited amounts of blood, but that is a horrific procedure and not one that I recommend for anyone outside the newborn-first month of life period.

This is the challenge, getting the blood and getting sufficient amount of serum.

Other thoughts? Let's think hard. What more can we do for FDA and industry in coming up with ideas here for postlicensure? I am sure we will think of a lot of things tonight over dinner, and if we do we can bring them up again to you.

DR. DURBIN: Going forward, it looks like the vaccine schedule is of course going to have to be evaluated in the context of other vaccines that will be given. So I think those are some important studies that will have to be done.

DR. FERRIERI: But the concept of being this far along with any meningococcal serogroup B vaccines is very exciting for those of us who kept asking every year, will there ever be serogroup B vaccines. So it is just fantastic to be in this position, discussing the subject, I think.

Other ideas or thoughts from our group here? Dr. Gellin, do you have anything you would like to add at this point? Why don't I go around the room and ask around the table? Dr. Cheung, is there anything you would like to add to what we have said?

DR. CHEUNG: It seems like we had a very thorough discussion on the issues about postlicensure studies. I think you mentioned that it is difficult to do in terms of blood drawing, but given the seriousness of disease, they should be done. I don't think we should just extrapolate.

DR. FERRIERI: Thank you. Dr. Gilbert, any further words?

DR. GILBERT: Yes, maybe just to amplify a point that I started to make. Given that it may take awhile to get data on lots of vaccine breakthrough in infants under two and to try to see if they tend to have lack of antibody response, in the meantime it might be of high value to fill in the gap that I am hearing. Even in pre vaccination, even in infants zero to two, we don't have much data on how anti-bactericidal titer correlates with disease. That might be a hole that can be filled in relatively cheaply and quickly.

DR. FERRIERI: Thank you very much.

DR. APICELLA: It is the long term response to the vaccine. If you look at the literature in infants, it falls off pretty rapidly even after multiple doses of vaccine.

I think a long, long term question is, how does this impact on the next period of life when they are susceptible at age 16 again to the disease; should they be revaccinated, and should it be a full course of vaccination. But that is the long term.

DR. FERRIERI: Yes, long term. That is a very critical point. Then I should go to Dr. Reynolds, please.

DR. REYNOLDS: I think the core of effectiveness should be what CDC is doing now with the adolescents. That is a case control study. I agree with following antibody levels also.

DR. FERRIERI: Thank you. Dr. McInnes? Dr. Schoolnik, anything you would like to add?

DR. SCHOOLNIK: Just to make an observation. One of the most remarkable things about this afternoon is the frequency with which we refer to Irving Goldschneider's paper, which if I recall was published in the *Journal of Experimental Medicine* about 1969, something like that. Yet we are in an era of genomics, high throughput omics of all kinds.

I am struck by both the rigor of the vaccinology that I see demonstrated here by the FDA and by the manufacturers that we will hear from, I'm sure, more tomorrow. But also I have this sense that somehow vaccinology is stuck. I am waiting to hear what the new science might contribute to all of this, and I am not hearing it today. Yet many of us in the room who are in academic life are busily engaged sequencing genomes, doing full genomic functional studies, doing systems biology actually.

At Stanford we have something called a human immune monitoring core, where we are trying to predict efficacy in vaccination recipients based on a whole array of immune correlates. It is just an observation that I am making. There is nothing wrong with it. We are developing and using effective vaccines using something that is 40 years old. But it is a little surprising to me.

DR. FERRIERI: I think that is another conference, Gary, new trends in vaccinology. I agree completely that this is not where we are right today for this round of the serogroup B meninge.

DR. TACKET: I love your comments, Gary, but nothing beats a good field trial.

DR. GRAY: Let me pitch one more try at this carriage. If we think about how the conjugate pneumococcal vaccine impacted pneumococcal disease and the ecology of the strains

It would seem to me appropriate to similarly study the carriage of this bacteria B, particularly in the age group we are interested in. It is not an invasive procedure, in the sense that even a heel stick is; it is a throat swab. If we had an idea that there was a massive change in the relative prevalence with respect to vaccination, that might tell us something new. It seems to me worth doing.

DR. FERRIERI: I like prevalence studies of that kind. Thank you very much for that suggestion. I don't know if FDA or industry likes it.

I had always learned that colonization was relatively due to any of the meningococcal serogroups. A little bit of that data was presented earlier today. So it might be of interest, realizing you would have to do a very big survey because the numbers are so low out there.

But I still like doing that sort of thing. We will recruit you to do it, too.

Luckily I have Dawn here at my right side coaching me. Does FDA have any questions for us? Would FDA like more from us right now? How do you feel about, Dr. Baylor, where we are at the moment with these two discussion points?

DR. BAYLOR: I think this has been a very fruitful discussion. I wanted to thank everybody on the committee.

I think we came to you today because we are getting into an area where it is going to be very difficult to do vaccine efficacy studies for diseases where the incidence is low. We are trying to facilitate the movement and development of these vaccines.

There is a question as Dr. Gellin had commented on about licensing a vaccine and then recommendations for the vaccine. We are here today to try to facilitate the development and licensure of these vaccines. We are presenting what we have tried to come up with as far as alternatives to clinical efficacy studies when they can't be done. So it was very important for us to hear your comments on what we are proposing. So it has been very valuable to hear that discussion and get confirmation that we are to some extent on the right track of trying to develop these pathways. You will hear more of that tomorrow as well, but this has been a very fruitful discussion. Thank you.

DR. FERRIERI: Thank you. I think that we are at a close for today. I remind everyone that tomorrow morning we start at 8:30 sharp. So thanks for everyone's contributions.

(Whereupon, the meeting was recessed, to reconvene Thursday, April 7, at 8:30 a.m.)